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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/47, A61K 38/17

A3

(11) International Publication Number: **WO 98/40404**

(43) International Publication Date: 17 September 1998 (17.09.98)

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(22) International Filing Date: 9 March 1998 (09.03.98)

(30) Priority Data:

08/815,381	11 March 1997 (11.03.97)	US
09/036,321	6 March 1998 (06.03.98)	US

(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 90 Green Meadow Drive, Tewksbury, MA 01876 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). AGOSTINO, Michael, J.; 26 Wolcott Avenue, Andover, MA 01810 (US).

(74) Agent: SPRUNGER, Suzanne, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
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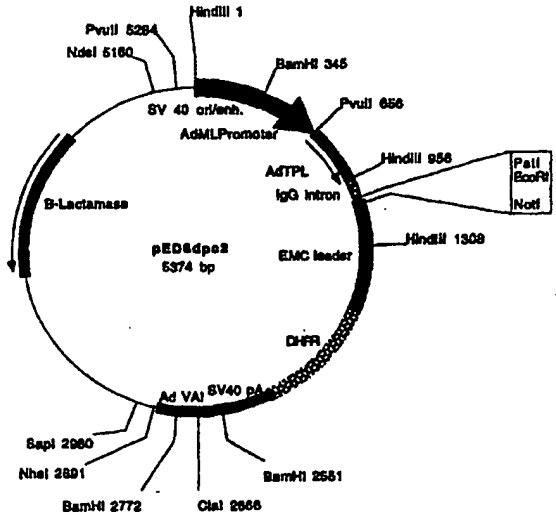
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
30 December 1998 (30.12.98)

(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 98/04601

A. CLASSIFICATION F SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 07198 A (GENETICS INST) 27 February 1997 see the whole document ---	1-11
A	US 5 536 637 A (K. JACOBS) 16 July 1996 cited in the application see the whole document --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1998	03. 11. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) D CUMENTS CONSIDERED T BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Y. FUJIOKA ET AL.,: "A novel membrane glycoprotein, SHPS-1, that binds the SH2-domain-containing protein tyrosine phosphatase SHP-2 in response to mitogens and cell adhesion" MOLECULAR AND CELLULAR BIOLOGY, vol. 16, no. 12, 1996, WASHINGTON, DC, US, pages 6887-6899, XP002072087 cited in the application see the whole document and specially Figure 4 ---	1,13
P,X	DATABASE NUCLEOTIDE PROTEIN SEQUENCE, - 28 October 1997 HINXTON, GB, XP002072088 AC= AA625610 similar to WP:K10B2.1 CE02008 transducin beta-chain ---	1,11
P,X	DATABASE NUCLEOTIDE PROTEIN SEQUENCE, - 6 February 1998 HINXTON, GB, XP002072072 AC= AA778577 similar to human TR:P78324 SHPS-1 ---	1,11
T	DATABASE NUCLEOTIDE PROTEIN SEQUENCE, - 15 March 1998 HINXTON, GB, XP002072089 AC= AA861049 similar to human TR:P78324 SHPS-1 ---	1,11
T	DATABASE NUCLEOTIDE PROTEIN SEQUENCE, - 15 March 1998 XP002072090 AC= AA862667 similar to human TR:P78324 SHPS-1 -----	1,11

2

INTERNATIONAL SEARCH REPORT

Ir ıational application No.
PCT/US 98/ 04601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see further information sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13

   Polynucleotide comprising the nucleotide sequence of SEQ.ID.N.1 and encoding a polypeptide of SEQ.ID.N.2. Polynucleotide fragments, variants, homologues and gene thereof. Host cells transformed with said polynucleotide. Protein comprising SEQ.ID.N.2 or fragments thereof. Pharmaceutical compositions.

2. Claims: 14-16

   As invention 1 but concerning SEQ.ID.N.3, 4 and 31

3. Claims: 17-19

   As invention 1 but concerning SEQ.ID.N.5 and 6

4. Claims: 20-22

   As invention 1 but concerning SEQ.ID.N.7 and 8

5. Claims: 23-25

   As invention 1 but concerning SEQ.ID.N.9 and 10

6. Claims: 26-28

   As invention 1 but concerning SEQ.ID.N.11 and 12

7. Claims: 29-31

   As invention 1 but concerning SEQ.ID.N.13 and 14

8. Claims: 32-34

   As invention 1 but concerning SEQ.ID.N.15 and 16

9. Claims: 35-37

   As invention 1 but concerning SEQ.ID.N.17 and 18

10. Claims: 38-40

    As invention 1 but concerning SEQ.ID.N.19 and 20

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 98/04601

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9707198 A	27-02-1997	US 5707829 A	13-01-1998
		AU 6712396 A	18-02-1997
		AU 6768596 A	12-03-1997
		EP 0839196 A	06-05-1998
		EP 0851875 A	08-07-1998
		WO 9704097 A	06-02-1997
US 5536637 A	16-07-1996	US 5712116 A	27-01-1998

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Published

Without international search report and to be republished upon receipt of that report.

(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

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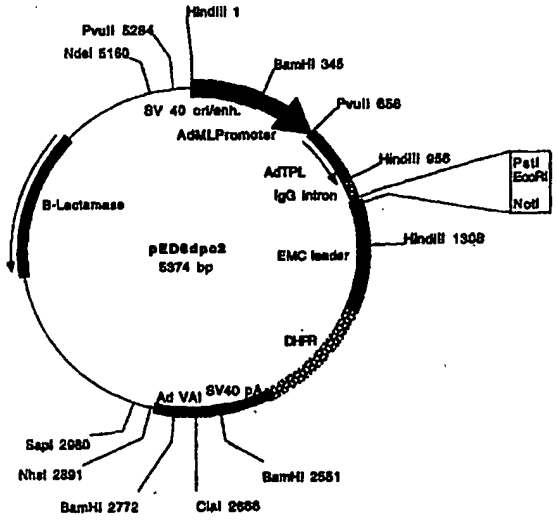

Plasmid name: pED6dpc2
Plasmid size: 5374 bp

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of Ser. No. 60/XXX,XXX (converted to a provisional application from non-provisional application Ser. No. 08/815,381), filed March 11, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 521 to nucleotide 1111;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 536 to nucleotide 817;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ax318_3 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone ax318_3 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 93 to amino acid 102 of SEQ ID NO:2;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 521 to nucleotide 1111; the nucleotide sequence of SEQ ID NO:1 from nucleotide 536 to nucleotide 817; the nucleotide sequence of the full-length protein

coding sequence of clone ax318_3 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone ax318_3 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 4 to amino acid 99.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 4 to amino acid 99;

(c) fragments of the amino acid sequence of SEQ ID NO:2 comprising the amino acid sequence from amino acid 93 to amino acid 102 of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 4 to amino acid 99.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 61 to nucleotide 864;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 826 to nucleotide 1386;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bg140_1 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bg140_1 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 129 to amino acid 138 of SEQ ID NO:4;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 61 to nucleotide 864; the nucleotide sequence of SEQ ID NO:3 from nucleotide 826 to nucleotide 1386; the nucleotide sequence of the full-length protein coding sequence of clone bg140_1 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone bg140_1 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:31 from amino acid 148 to amino acid 249.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:31;

(c) the amino acid sequence of SEQ ID NO:31 from amino acid 148 to amino acid 249;

(d) fragments of the amino acid sequence of SEQ ID NO:4 comprising the amino acid sequence from amino acid 129 to amino acid 138 of SEQ ID NO:4;

(e) fragments of the amino acid sequence of SEQ ID NO:31comprising the amino acid sequence from amino acid 163 to amino acid 172 of SEQ ID NO:31; and

(f) the amino acid sequence encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4, the amino acid sequence of SEQ ID NO:31, or the amino acid sequence of SEQ ID NO:31 from amino acid 148 to amino acid 249.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 77 to nucleotide 1624;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 390 to nucleotide 789;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bg465_2 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bg465_2 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 253 to amino acid 262 of SEQ ID NO:6;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 77 to nucleotide 1624; the nucleotide sequence of SEQ ID NO:5 from nucleotide 390 to nucleotide 789; the nucleotide sequence of the full-length protein coding sequence of clone bg465_2 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone bg465_2 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 260 to amino acid 343.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 260 to amino acid 343;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising the amino acid sequence from amino acid 253 to amino acid 262 of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 260 to amino acid 343.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 48 to nucleotide 1055;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 216 to nucleotide 1055;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 494 to nucleotide 958;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bk291_3 deposited under accession number ATCC 98353;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bk291_3 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 85 to amino acid 94 of SEQ ID NO:8;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 48 to nucleotide 1055; the nucleotide sequence of SEQ ID NO:7 from nucleotide 216 to nucleotide 1055; the nucleotide sequence of SEQ ID NO:7 from nucleotide 494 to nucleotide 958; the nucleotide sequence of the full-length protein coding sequence of clone bk291_3 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone bk291_3 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8 from amino acid 188 to amino acid 306.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 188 to amino acid 306;

(c) fragments of the amino acid sequence of SEQ ID NO:8 comprising the amino acid sequence from amino acid 85 to amino acid 94 of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 188 to amino acid 306.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 64 to nucleotide 1197;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 828;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bp537_4 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bp537_4 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:10;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 64 to nucleotide 1197; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 828; the nucleotide sequence of the full-length protein coding sequence of clone bp537_4 deposited under accession number ATCC 98353; or the

nucleotide sequence of the mature protein coding sequence of clone bp537_4 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 255.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 255;

(c) fragments of the amino acid sequence of SEQ ID NO:10 comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 255.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 581 to nucleotide 1534;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 928 to nucleotide 1510;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cs431_2 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cs431_2 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 154 to amino acid 163 of SEQ ID NO:12;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 581 to nucleotide 1534; the nucleotide sequence of SEQ ID NO:11 from nucleotide 928 to nucleotide 1510; the nucleotide sequence of the full-length protein coding sequence of clone cs431_2 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone cs431_2 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 150 to amino acid 310.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 150 to amino acid 310;

(c) fragments of the amino acid sequence of SEQ ID NO:12 comprising the amino acid sequence from amino acid 154 to amino acid 163 of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 150 to amino acid 310.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 29 to nucleotide 2227;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1334 to nucleotide 2227;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 746;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cw976_1 deposited under accession number ATCC 98353;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cw976_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 361 to amino acid 370 of SEQ ID NO:14;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 29 to nucleotide 2227; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1334 to nucleotide 2227; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 746; the nucleotide sequence of the full-length protein coding sequence of clone cw976_1 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone cw976_1 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 239, or a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 119 to amino acid 733.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 239;

(c) the amino acid sequence of SEQ ID NO:14 from amino acid 119 to amino acid 733;

(d) fragments of the amino acid sequence of SEQ ID NO:14 comprising the amino acid sequence from amino acid 361 to amino acid 370 of SEQ ID NO:14; and

(e) the amino acid sequence encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14, the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 239, or the amino acid sequence of SEQ ID NO:14 from amino acid 119 to amino acid 733.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 364 to nucleotide 777;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 636;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cw1233_3 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cw1233_3 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment

comprising the amino acid sequence from amino acid 64 to amino acid 73 of SEQ ID NO:16;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 364 to nucleotide 777; the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 636; the nucleotide sequence of the full-length protein coding sequence of clone cw1233_3 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone cw1233_3 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 91.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 91;

(c) fragments of the amino acid sequence of SEQ ID NO:16 comprising the amino acid sequence from amino acid 64 to amino acid 73 of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 91.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 619 to nucleotide 1434;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 520 to nucleotide 1323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone dg1_1 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone dg1_1 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 131 to amino acid 140 of SEQ ID NO:18;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 619 to nucleotide 1434; the nucleotide sequence of SEQ ID NO:17 from nucleotide 520 to nucleotide 1323; the nucleotide sequence of the full-length protein coding sequence of clone dg1_1 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone dg1_1 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 235.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 235;

(c) fragments of the amino acid sequence of SEQ ID NO:18 comprising the amino acid sequence from amino acid 131 to amino acid 140 of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 235.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2063 to nucleotide 2290;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2276 to nucleotide 2290;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2037 to nucleotide 2405;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ep234_1 deposited under accession number ATCC 98353;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ep234_1 deposited under accession number ATCC 98353;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone ep234_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone ep234_1 deposited under accession number ATCC 98353;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:20;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 2063 to nucleotide 2290; the nucleotide sequence of SEQ ID NO:19 from nucleotide 2276 to nucleotide 2290; the nucleotide sequence of SEQ ID NO:19 from nucleotide 2037 to nucleotide 2405; the nucleotide sequence of the full-length protein coding sequence of clone ep234_1 deposited under accession number ATCC 98353; or the nucleotide sequence of the mature protein coding sequence of clone ep234_1 deposited under accession number ATCC 98353. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of

clone ep234_1 deposited under accession number ATCC 98353. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 69.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 69;

(c) fragments of the amino acid sequence of SEQ ID NO:20 comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone ep234_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 69.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "ax318_3"

A polynucleotide of the present invention has been identified as clone "ax318_3". ax318_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ax318_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ax318_3 protein").

The nucleotide sequence of ax318_3 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ax318_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ax318_3 should be approximately 1200 bp.

The nucleotide sequence disclosed herein for ax318_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ax318_3 demonstrated at least some similarity with sequences identified as AA255872 (zs19a01.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone), AA625610 (zv89h04.s1 Soares NhHMPu S1 Homo sapiens cDNA clone 766999 3' similar to WP:K10B2.1 CE02008 TRANSDUCIN BETA CHAIN), D86043 (Human mRNA for SHPS-1, complete cds), H23217 (ym52f03.s1 Homo sapiens cDNA clone 51880 3'), U06701 (Human clone CCA53 mRNA containing CCA trinucleotide repeat), and W05822 (za90b02.r1 Soares fetal lung NbHL19W Homo sapiens cDNA clone 299787 5'). The predicted amino acid sequence disclosed herein for ax318_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted ax318_3 protein demonstrated at least some similarity to sequences identified as D85183 (SHPS-1 [Rattus rattus]), D86043 (SHPS-1 [Homo sapiens]), R85852 (WD-40 domain-containing beta-transducin protein), Y10376 (SIRP-beta1 [Homo sapiens]), and Z79757 (F55B12.3 [Caenorhabditis elegans]). SHPS-1 is a membrane glycoprotein that binds the SH2-domain-containing protein tyrosine phosphatase SHP-2 in response to mitogens and cell adhesion (Fujioka *et al.*, 1996, *Mol. Cell. Biol.* **16(12)**: 6887-6899, incorporated by reference herein). Based upon sequence similarity, ax318_3 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a putative transmembrane domain within the ax318_3 protein sequence, centered around amino acid 28 of SEQ ID NO:2; amino acids 15 to 27 of SEQ ID NO:2 are

also a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 28.

Clone "bg140_1"

A polynucleotide of the present invention has been identified as clone "bg140_1". bg140_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bg140_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bg140_1 protein").

The nucleotide sequence of bg140_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bg140_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Another possible bg140_1 reading frame and predicted amino acid sequence, encoded by base pairs 641 to 1648 of SEQ ID NO:3, is reported in SEQ ID NO:31. A frameshift in the nucleotide sequence of SEQ ID NO:3, caused, for example, by a single base pair deletion near position 825 of SEQ ID NO:3, could join the open reading frame encoding SEQ ID NO:4 with that encoding SEQ ID NO:31.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bg140_1 should be approximately 2900 bp.

The nucleotide sequence disclosed herein for bg140_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bg140_1 demonstrated at least some similarity with sequences identified as AA075629 (zm89a04.s1 Stratagene ovarian cancer (#937219) Homo sapiens cDNA clone 545070 3'), AA113989 (zn27h12.r1 Stratagene neuroepithelium NT2RAMI 937234 Homo sapiens cDNA clone 548711 5'), N77135 (yz85h11.r1 Homo sapiens cDNA clone 289893 5'), R11701 (yf49d02.r1 Homo sapiens cDNA clone 25600 5'), R13178 (yf73e04.r1 Homo sapiens cDNA clone 27855 5'), and Y14946 (Homo sapiens mRNA for SPIN protein). The predicted amino acid sequence disclosed herein for bg140_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted bg140_1 protein demonstrated at least some similarity to sequences identified as AF038969 (general transcription factor 2-I [Homo

sapiens]), U77948 (Bruton's tyrosine kinase-associated protein-135; BAP-135 [Homo sapiens]), and Y14946 (SPIN protein [Homo sapiens]). Based upon sequence similarity, bg140_1 proteins and each similar protein or peptide may share at least some activity.

Clone "bg465_2"

A polynucleotide of the present invention has been identified as clone "bg465_2". bg465_2 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bg465_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bg465_2 protein").

The nucleotide sequence of bg465_2 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bg465_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bg465_2 should be approximately 2500 bp.

The nucleotide sequence disclosed herein for bg465_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bg465_2 demonstrated at least some similarity with sequences identified as AA133150 (zm25b07.r1 Stratagene pancreas (#937208) Homo sapiens cDNA clone 526645 5' similar to WP:F07F6.4 CE01896 ZINC FINGER PROTEIN), AA144842 (mr69h01.r1 Stratagene mouse testis (#937308) Mus musculus cDNA clone 602737 5'), AA484561 (nf06a12.s1 NCI_CGAP_Li1 Homo sapiens cDNA clone), D16939 (Human HepG2 3' region cDNA, clone hmd5d06), L24125 (Saccharomyces cerevisiae zinc finger protein (GCS1) gene, complete cds), R18422 (yg02f06.r1 Homo sapiens cDNA clone 30950 5'), T32543 (EST50558 Homo sapiens cDNA 5' end similar to None), W88569 (zh70b12.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 417407 3'), Z74274 (S.cerevisiae chromosome IV reading frame ORF YDL226c), and Z82199 (Human DNA sequence *** SEQUENCING IN PROGRESS *** from clone 316D5; HTGS phase 1). The predicted amino acid sequence disclosed herein for bg465_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted bg465_2 protein demonstrated at least some similarity to sequences

identified as U23486 (similar to S. cerevisiae zinc finger protein GCS1 (SP GCS1_YEAST) [Caenorhabditis elegans]). Based upon sequence similarity, bg465_2 proteins and each similar protein or peptide may share at least some activity.

Clone "bk291_3"

A polynucleotide of the present invention has been identified as clone "bk291_3". bk291_3 was isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bk291_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bk291_3 protein").

The nucleotide sequence of bk291_3 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bk291_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8. Amino acids 44 to 56 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 57, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bk291_3 should be approximately 1500 bp.

The nucleotide sequence disclosed herein for bk291_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bk291_3 demonstrated at least some similarity with sequences identified as AA135915 (zl19f04.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 502399 5'), AA156738 (zl19f04.s1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 502399 3' similar to WP:T05E11.5 CE06364 YEAST YKK0 LIKE), AF017785 (Mus musculus MHC Class I H13a minor histocompatibility peptide (H13) mRNA, partial cds), N40134 (yw73a12.r1 Homo sapiens cDNA clone 257854 5' similar to SW:YKK0_YEAST P34248 HYPOTHETICAL 67.5 KD PROTEIN IN APE1/LAP4-CWP1 INTERGENIC REGION), N42726 (yy11d01.r1 Homo sapiens cDNA clone 270913 5' similar to SW:YKK0_YEAST P34248 HYPOTHETICAL 67.5 KD PROTEIN IN APE1/LAP4-CWP1 INTERGENIC REGION), R67144 (yi31h04.r1 Homo sapiens cDNA clone 140887 5' similar to SP:YKK0_YEAST P34248 HYPOTHETICAL 67.5 KD PROTEIN IN APE1/LAP4-MBR1 INTERGENIC), R78822 (yi90b05.r1 Homo sapiens cDNA clone 146481 5'), R79317

(yi90b05.s1 Homo sapiens cDNA clone 146481 3'), T23944 (Human gene signature HUMGS05889), and W04243 (za58h10.r1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone). The predicted amino acid sequence disclosed herein for bk291_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted bk291_3 protein demonstrated at least some similarity to sequences identified as X71133 (YKL450 [Saccharomyces cerevisiae]), Z28100 (ORF YKL100c [Saccharomyces cerevisiae]), and Z68751 (T05E11.5 [Caenorhabditis elegans]). Based upon sequence similarity, bk291_3 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts six additional potential transmembrane domains within the bk291_3 protein sequence, centered around amino acids 70, 125, 170, 220, 260, and 280 of SEQ ID NO:8.

Clone "bp537_4"

A polynucleotide of the present invention has been identified as clone "bp537_4". bp537_4 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bp537_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bp537_4 protein").

The nucleotide sequence of bp537_4 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bp537_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bp537_4 should be approximately 1500 bp.

The nucleotide sequence disclosed herein for bp537_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bp537_4 demonstrated at least some similarity with sequences identified as AA007576 (zh99b06.r1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 429395 5'), AA287563 (zs52g02.r1 NCI_CGAP_GCB1 Homo sapiens cDNA 5'), R09093 (yf21h09.r1 Homo sapiens cDNA clone 127553 5'), and T33088 (EST56631 Homo sapiens cDNA 5' end similar to None). The predicted amino acid sequence disclosed herein for bp537_4 was searched against the GenPept and GeneSeq amino acid

sequence databases using the BLASTX search protocol. The predicted bp537_4 protein demonstrated at least some similarity to sequences identified as U34998 (Rad9 [Coprinus cinereus]). Based upon sequence similarity, bp537_4 proteins and each similar protein or peptide may share at least some activity.

Clone "cs431_2"

A polynucleotide of the present invention has been identified as clone "cs431_2". cs431_2 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cs431_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cs431_2 protein").

The nucleotide sequence of cs431_2 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the cs431_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cs431_2 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for cs431_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cs431_2 demonstrated at least some similarity with sequences identified as AA021033 (ze67h12.s1 Soares retina N2b4HR Homo sapiens cDNA clone 364103 3' similar to contains Alu repetitive element), H29349 (ym32c02.r1 Homo sapiens cDNA clone 49839 5' similar to SP:KYES_XIPHE P27447 PROTO-ONCOGENE TYROSINE-PROTEIN KINASE YES), L14577 (Homo sapiens cystathionine beta-synthase (CBS) mRNA, complete cds), Q87430 (Human cystathionine beta-synthase cDNA), and X92659 (H.sapiens intron 4 from p53 gene). The predicted amino acid sequence disclosed herein for cs431_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted cs431_2 protein demonstrated at least some similarity to sequences identified as L19501 (cystathionine beta-synthase [Homo sapiens]), R71376 (Human cystathionine beta-synthase), U61167 (SH3 domain-containing protein SH3P18 [Homo sapiens]), and X82166 (cystathionine beta-synthase [Homo sapiens]). Based upon sequence similarity, cs431_2 proteins and

each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the cs431_2 protein sequence centered around amino acid 30 of SEQ ID NO:12. The nucleotide sequence of cs431_2 indicates that it may contain an Alu repetitive element.

Clone "cw976_1"

A polynucleotide of the present invention has been identified as clone "cw976_1". cw976_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cw976_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cw976_1 protein").

The nucleotide sequence of cw976_1 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the cw976_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Amino acids 423 to 435 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 436, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cw976_1 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for cw976_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cw976_1 demonstrated at least some similarity with sequences identified as AA280747 (zs96a09.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:711448 5'), AA323946 (EST26798 Cerebellum II Homo sapiens cDNA 5' end), R13665 (yf60g06.r1 Homo sapiens cDNA clone 26764 5'), R16892 (yf44d06.s2 Homo sapiens cDNA clone 129707 3'), R85177 (yo43d07.r1 Homo sapiens cDNA clone 180685 5'), and R89648 (ym97c02.r1 Homo sapiens cDNA clone 166850 5'). Based upon sequence similarity, cw976_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the cw976_1 protein sequence at the amino terminus of SEQ ID NO:14.

Clone "cw1233_3"

A polynucleotide of the present invention has been identified as clone "cw1233_3". cw1233_3 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cw1233_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cw1233_3 protein").

The nucleotide sequence of cw1233_3 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the cw1233_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cw1233_3 should be approximately 3000 bp.

The nucleotide sequence disclosed herein for cw1233_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cw1233_3 demonstrated at least some similarity with sequences identified as R61600 (yh16f08.r1 Homo sapiens cDNA clone 37807 5'), R83929 (yp06h11.s1 Homo sapiens cDNA clone 186693 3' similar to contains Alu repetitive element;contains TAR1 repetitive element), R87877 (yo45h05.r1 Homo sapiens cDNA clone 180921 5'), U14568 (***ALU WARNING Human Alu-Sb subfamily consensus sequence). The predicted amino acid sequence disclosed herein for cw1233_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted cw1233_3 protein demonstrated at least some similarity to sequences identified as AB002317 (KIAA0319 [Homo sapiens]). Based upon sequence similarity, cw1233_3 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of cw1233_3 indicates that it may contain an Alu repetitive element.

Clone "dg1_1"

A polynucleotide of the present invention has been identified as clone "dg1_1". dg1_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer

analysis of the amino acid sequence of the encoded protein. dg1_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "dg1_1 protein").

The nucleotide sequence of dg1_1 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the dg1_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone dg1_1 should be approximately 1900 bp.

The nucleotide sequence disclosed herein for dg1_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. dg1_1 demonstrated at least some similarity with sequences identified as AA731281 (nw57f05.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE 1250721 similar to gb Y00345_cds1 POLYADENYLATE-BINDING PROTEIN (HUMAN)). The predicted amino acid sequence disclosed herein for dg1_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted dg1_1 protein demonstrated at least some similarity to sequences identified as M81878 (hyaluronidase [Clostridium perfringens]) and U28742 (similar to hyaluronoglucosaminidase (SPNAGH_CLOPE, P26831) [Caenorhabditis elegans]). Hyaluronoglucosaminidase is a secreted protein found, for example, in bee venom. Based upon sequence similarity, dg1_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the dg1_1 protein sequence centered around amino acid 150 of SEQ ID NO:18.

Clone "ep234_1"

A polynucleotide of the present invention has been identified as clone "ep234_1". ep234_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ep234_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ep234_1 protein").

The nucleotide sequence of ep234_1 as presently determined is reported in SEQ ID NO:19. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ep234_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 59 to 71 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 72, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ep234_1 should be approximately 2500 bp.

The nucleotide sequence disclosed herein for ep234_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ep234_1 demonstrated at least some similarity with sequences identified as AA044714 (zf54d09.r1 Soares retina N2b4HR Homo sapiens cDNA clone 380753 5'), AA454840 (zx79d09.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 809969 3'), AA470137 (zu11e01.s1 Soares testis NHT Homo sapiens cDNA clone 731544 3'), H24852 (yl42c11.r1 Homo sapiens cDNA clone 160916 5'), N64648 (yz87b06.s1 Homo sapiens cDNA clone 290003 3'), R45788 (Ha662-f Homo sapiens cDNA clone a662-f), T70546 (yd15b07.s1 Homo sapiens cDNA clone 108277 3'), W73481 (zd54e01.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 344472 3'), and W73553 (zd54e01.r1 Soares fetal heart). Based upon sequence similarity, ep234_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts at least two potential transmembrane domains within the ep234_1 protein sequence of SEQ ID NO:20.

Deposit of Clones

Clones ax318_3, bg140_1, bg465_2, bk291_3, bp537_4, cs431_2, cw976_1, cw1233_3, dg1_1, and ep234_1 were deposited on March 11, 1997 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98353, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the

appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* **19**: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* **9**: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
ax318_3	SEQ ID NO:21
bg140_1	SEQ ID NO:22
bg465_2	SEQ ID NO:23, SEQ ID NO:32
bk291_3	SEQ ID NO:24
bp537_4	SEQ ID NO:25
cs431_2	SEQ ID NO:26
cw976_1	SEQ ID NO:27
cw1233_3	SEQ ID NO:28
dg1_1	SEQ ID NO:29
ep234_1	SEQ ID NO:30

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a

nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed

by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can

be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* **15(7)**: 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* **62(1)**: 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* **58**: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* **14(9)**: 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* **90(16)**: 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* **91(2)**: 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* **336**: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of

assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologs are those isolated from mammalian species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides .

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed

to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205

cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.,* Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as

those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art

(see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that

described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in*

Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the

molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and

murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary

costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro*

antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell

lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and

Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in

circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-

β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion

include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without

limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human

diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from

forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms;

effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects

of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active

ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein

of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such

antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and

polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Merberg, David
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 32

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: U.S.A.
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Sprunger, Suzanne A.
(B) REGISTRATION NUMBER: 41,323

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617) 498-8284
(B) TELEFAX: (617) 876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1328 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGTTAACAAG TGGAATGGAA CTCAAAGACA ATATTCTTGT CTCTGGGAAT GCAGATTCTA 60

CAGTTAAAAT CTGGGATATC AAAACAGGAC AGTGTTTACA AACATTGCAA GGTCCCAACA 120

AGCATCAGAG TGCTGTGACC TGTTTACAGT TCAACAAGAA CTTTGTAATT ACCAGCTCAG 180

ATGATGGAAC TGTAAAACTA TGGGACTTGA AAACGGGTGA ATTTATTCGA AACCTAGTCA 240

CATTGGAGAG TGGGGGGAGT GGGGGAGTTG TGTGGCGGAT CACAGCCTCA AACACAAAGC 300

TGGTGTGTGC AGTTGGGAGT CGGAATGGGA CTGAAGAAAC CAAGCTGCTG GTGCTGGACT 360

TTGATGTGGA CATGAAGTGA AGAGCAGAAA AGATGAATTT GTCCAATTGT GTAGACGATA 420

TACTCCCTGC CCTTCCCCCT GCAAAAAGAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 480

AAAAAAAAAA AAAAAAGCGC AAGCTCCAGG TTTCACCACA ATGCCCATCC CTGCCTCCCC 540

ACTCCACCCA CCTCTGCCTT CCTTACTGCT GTATCTGCTG CTTGAACTGG CAGGAGTCAC 600

ACATGTGTTC CATGTGCAAC AAACGGAGAT GTCACAGACT GTATCAACTG GGGAGTCAAT 660

CATCTTGAGT TGCAGCGTAC CCGATACCTT ACCAAATGGA CCTGTCTTGT GGTTCAAGGG 720

AACAGGGCCA AACCGGAAAT TAATCTACAA TTTCAAACAA GGTAACTTTC CCAGAGTAAA 780

AGAGATTGGA GACACCACCA AGCCTGGCAA CACAGACTTT TCCACCCGCA TCCGTGAAAT 840

CTCTCTTGCT GATGCTGGCA CCTATTACTG CGTGAAGTTC ATAAAAGGAA GAGCTATCAA 900

GGAGTACCAA TCAGGTCGGG GCACTCAGGT GTTTGTTACT GAGCAGAATC CAAGACCTCC 960

CAAGAACAGA CCTGCAGGCA GAGCAGGCTC CAGGGCCCAC CATGATGCCC ATACCTGCCT 1020

CTCGGCCCTG CCTGAGAGAA ACAGCACAAA CTATTTCGTC CAACCCTGCT GCTGCCTCCG 1080

GCTGCTGGGA CTCACAGGCT TGCTGTCAAA ATAATCCAAA CAGGGAAGGA ACGTACAAGT 1140

AAATAACAAA AGCCCCCATA CTCTTCTGAC TCCCTGGAGA CAGCTACTTT TTAGGAGTTT 1200

CATTTGCCTT CTTCAAGAGA GCTTTCTTCC ACTGACATAA AATGCCAGCT TGATCGTACA 1260

ATAAATCTGT CTATTTACCT GGGTCCAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1320

AAAAAAAA 1328

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 197 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Pro Ile Pro Ala Ser Pro Leu His Pro Pro Leu Pro Ser Leu Leu
1               5                  10                  15

Leu Tyr Leu Leu Leu Glu Leu Ala Gly Val Thr His Val Phe His Val
            20                  25                  30

Gln Gln Thr Glu Met Ser Gln Thr Val Ser Thr Gly Glu Ser Ile Ile
        35                  40                  45

Leu Ser Cys Ser Val Pro Asp Thr Leu Pro Asn Gly Pro Val Leu Trp
    50                  55                  60

Phe Lys Gly Thr Gly Pro Asn Arg Lys Leu Ile Tyr Asn Phe Lys Gln
65                  70                  75                  80

Gly Asn Phe Pro Arg Val Lys Glu Ile Gly Asp Thr Thr Lys Pro Gly
                85                  90                  95

Asn Thr Asp Phe Ser Thr Arg Ile Arg Glu Ile Ser Leu Ala Asp Ala
            100                 105                 110

Gly Thr Tyr Tyr Cys Val Lys Phe Ile Lys Gly Arg Ala Ile Lys Glu
        115                 120                 125

Tyr Gln Ser Gly Arg Gly Thr Gln Val Phe Val Thr Glu Gln Asn Pro
    130                 135                 140

Arg Pro Pro Lys Asn Arg Pro Ala Gly Arg Ala Gly Ser Arg Ala His
145                 150                 155                 160

His Asp Ala His Thr Cys Leu Ser Ala Leu Pro Glu Arg Asn Ser Thr
                165                 170                 175

Asn Tyr Phe Val Gln Pro Cys Cys Cys Leu Arg Leu Leu Gly Leu Thr
            180                 185                 190

Gly Leu Leu Ser Lys
        195
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2835 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GCTTGATAAG CCAGCTTCAG GAGTAAAGGA AGAATGGTAT GCCAGAATCA CTAAATTAAG 60

ATGGTGGATC AGCTTTTCTG CAAAAAATTT GCGGAAGCCT TGGGGAGCAC TGAAGCCAAG 120

GCTGTACCGT ACCAAAAATT TGAGGCACAC CCGAATGATC TGTACGTGGA AGGACTGCCA 180

GAAAACATTC CTTTCCGAAG TCCCTCATGG TATGGAATCC CAAGGCTGGA AAAAATCATT 240

CAAGTGGGCA ATCGAATTAA ATTTGTTATT AAAAGACCAG AACTTCTGAC TCACAGTACC 300

ACTGAAGTTA CTCAGCCAAG AACGAATACA CCAGTCAAAG AAGATTGGAA TGTCAGAATT 360

ACCAAGCTAC GGAAGCAAGT GGAAGAGATT TTTAATTTGA AATTTGCTCA AGCTCTTGGA 420

CTCACCGAGG CAGTAAAAGT ACCATATCCT GTGTTTGAAT CAAACCCGGA GTTCTTGTAT 480

GTGGAAGGCT TGCCAGAGGG GATTCCCTTC CGAAGCCCTA CCTGGTTTGG AATTCCACGA 540

CTTGAAAGGA TCGTCCACGG GAGTAATAAA ATCAAGTTCG TTGTTAAAAA ACCTGAACTA 600

GTTATTTCCT ACTTGCCTCC TGGGATGGCT AGTAAAATAA ACACTAAAGC TTTGCAGTCC 660

CCCAAAAGAC CACGAAGTCC TGGGAGTAAT TCAAAGGTTC CTGAAATTGA GGTCACCGTG 720

GAAGGCCYTA ATAACAACAA TCCTCAAACC TCAGCTGTTC GAACCCCGAC CCAGACTAAC 780

GGTTCTAACG TTCCCTTCAA GCCACGAGGG AGAGAGTTTT CCTTTGGCCT GGAATGCCAA 840

AATCACGGAC CTAAAACAGA AAGTTGAAAA TCTCTTCAAT GAGAAATGTG GGGAAGCTCT 900

TGGCCTTAAA CAAGCTGTGA AGGTGCCGTT CGCGTTATTT GAGTCTTTCC CGGAAGACTT 960

TTATGTGGAA GGCTTACCTG AGGGTGTGCC ATTCCGAAGA CCATCGACTT TTGGCATTCC 1020

GAGGCTGGAG AAGATACTCA GAAACAAAGC CAAAATTAAG TTCATCATTA AAAAGCCCGA 1080

AATGTTTGAG ACGGCGATTA AGGAGAGCAC CTCCTCTAAG AGCCCTCCCA GAAAAATAAA 1140

TTCATCACCC AATGTTAATA CTACTGCATC AGGTGTTGAA GACCTTAACA TCATTCAGGT 1200

GACAATTCCA GATGATGATA ATGAAAGACT CTCGAAAGTT GAAAAAGCTA GACAGCTAAG 1260

AGAACAAGTG AATGACCTCT TTAGTCGGAA ATTTGGTGAA GCTATTGGTA TGGGTTTTCC 1320

TGTGAAAGTT CCCTACAGGA AAATCACAAT TAACCCTGGC TGTGTGGTGG TTGATGGCAT 1380

GCCCCCGGGG GTGTCCTTCA AAGCCCCCAG CTACCTGGAA ATCAGCTCCA TGAGAAGGAT 1440

CTTAGACTCT GCCGAGTTTA TCAAATTCAC GGTCATTAGA CCATTTCCAG GACTTGTGAT 1500

TAATAACCAG CTGGTTGATC AGAGTGAGTC AAAAGGCCCC GTGATACAAG AATCAGCTGA 1560

ACCAAGCCAG TTGGAAGTTC CAGCCACAGA AGAAATAAAA GAGACTGATG GAAGCTCTCA 1620

GATCAAGCAA GAACCAGACC CCACGTGGTA GACCTCTTCC CTCCTAGGCT TAAAGTATCA 1680

GTGGTTGAGA AGAGCTTTTC GGACCTGTTA CTACCCCAAG CTGTGTAATA TACTTGTATA 1740

ACAGAAATAC CTTCTATACA AACCTTTTTT TCTACTTTTA GATAGAAATG TCTACTTTTT 1800

CAGCAGTTCT GTGAATTAAA GAGCAGAGTG ACTGTGGGTC TGGAATGGCT GGTGTACTTG 1860

GGAATGTACT ATCAGGATTT TACAGCAATG CTGGGAAATG ACAGGGAAAA TGACAGGAAT 1920

GAATCTCACC AGATTTTTTA TGTACTCAGC AGAGCCTTGA GTTACGGTGT TTATTTTCCA 1980

ATCAAGTGAA GATATCTCCT ACTTCTCCTA CTGGAACATC TCAGCTTCTG CAGTGAAGAA 2040

AAATTCCTGT GATAGTTCAG TTCTTTAGTT TTTCTATTTG AAAAAAAAAA ATCATTTAAA 2100

TGATCCTTTG TTCACGGCTC TCCTTAATGA CTGAGTGAAC AGTTCCTATC TGTATATTTG 2160

ACTAAACCTT TTCCTAAGCT ATCTCTCATG GTTCCTATGT TTTTTTATCA TAATTAAAAG 2220

CAAAACCATT TGGATCACCT AACAGTCAGA GGTCAGTATC TCAGCGTGTG AATTATAGAG 2280

GAAATACAGA GAGAACCTCT TCCACTTTTA CTTTTCGTCC AAATAAAATG CATGGTGTAC 2340

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CGCGGGACCT GCTGTGGCGC GGATTCTTAG GAACGCTGTT CTAGCCGGCC CCCTCTCCAG 2460

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GGAGTGAGGA GGGGTCAGGG GGCTAAGGAT GCAACCTCTG ACGTTCTGCG CCTTCCTAGG 2580

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GAATTATATG ACATGGTAGC AGAAATAGGC CCTTTTATGT GTTGCTTCTA TTTTACCTCA 2760

AATTGTAGAT ATAGGGTAAT CAATAAAATC CATCCATGCC TTTCAAAAAA AAAAAAAAAA 2820

AAAAAAAAAA AAAAA 2835

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 268 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met Val Asp Gln Leu Phe Cys Lys Lys Phe Ala Glu Ala Leu Gly Ser
1               5                  10                  15

Thr Glu Ala Lys Ala Val Pro Tyr Gln Lys Phe Glu Ala His Pro Asn
            20                  25                  30

Asp Leu Tyr Val Glu Gly Leu Pro Glu Asn Ile Pro Phe Arg Ser Pro
        35                  40                  45

Ser Trp Tyr Gly Ile Pro Arg Leu Glu Lys Ile Ile Gln Val Gly Asn
    50                  55                  60

Arg Ile Lys Phe Val Ile Lys Arg Pro Glu Leu Leu Thr His Ser Thr
65                  70                  75                  80

Thr Glu Val Thr Gln Pro Arg Thr Asn Thr Pro Val Lys Glu Asp Trp
                85                  90                  95

Asn Val Arg Ile Thr Lys Leu Arg Lys Gln Val Glu Glu Ile Phe Asn
            100                 105                 110

Leu Lys Phe Ala Gln Ala Leu Gly Leu Thr Glu Ala Val Lys Val Pro
        115                 120                 125

Tyr Pro Val Phe Glu Ser Asn Pro Glu Phe Leu Tyr Val Glu Gly Leu
    130                 135                 140

Pro Glu Gly Ile Pro Phe Arg Ser Pro Thr Trp Phe Gly Ile Pro Arg
145                 150                 155                 160

Leu Glu Arg Ile Val His Gly Ser Asn Lys Ile Lys Phe Val Val Lys
                165                 170                 175

Lys Pro Glu Leu Val Ile Ser Tyr Leu Pro Pro Gly Met Ala Ser Lys
            180                 185                 190

Ile Asn Thr Lys Ala Leu Gln Ser Pro Lys Arg Pro Arg Ser Pro Gly
        195                 200                 205

Ser Asn Ser Lys Val Pro Glu Ile Glu Val Thr Val Glu Gly Xaa Asn
    210                 215                 220

Asn Asn Asn Pro Gln Thr Ser Ala Val Arg Thr Pro Thr Gln Thr Asn
```

225 230 235 240

Gly Ser Asn Val Pro Phe Lys Pro Arg Gly Arg Glu Phe Ser Phe Gly
245 250 255

Leu Glu Cys Gln Asn His Gly Pro Lys Thr Glu Ser
260 265

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2705 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TAGGCCATGA AGGCCGCGCT TTTCGTCGAC TCTTACCGGT TGGCTGGGCC AGCTGCGCCG 60

CGGCTCACAG CTGACGATGG GGGACCCCAG CAAGCAGGAC ATCTTGACCA TCTTCAAGCG 120

CCTCCGCTCG GTGCCCACTA ACAAGGTGTG TTTTGATTGT GGTGCCAAAA ATCCCAGCTG 180

GGCAAGCATA ACCTATGGAG TGTTCCTTTG CATTGATTGC TCAGGGTCCC ACCGGTCACT 240

TGGTGTTCAC TTGAGTTTTA TTCGATCTAC AGAGTTGGAT TCCAACTGGT CATGGTTTCA 300

GTTGCGATGC ATGCAAGTCG GAGGAAACGC TAGTGCATCT TCCTTTTTTC ATCAACATGG 360

GTGTTCCACC AATGACACCA ATGCCAAGTA CAACAGTCGT GCTGCTCAGC TCTATAGGGA 420

GAAAATCAAA TCGCTCGCCT CTCAAGCAAC ACGGAAGCAT GGCACTGATC TGTGGCTTGA 480

TAGTTGTGTG GTTCCACCTT TGTCCCCTCC ACCAAAGGAG GAAGATTTTT TTGCCTCTCA 540

CGTTTCTCCT GAGGTGAGTG ACACAGCGTG GGCATCAGCA ATAGCAGAAC CATCTTCTTT 600

AACATCAAGG CCTGTGGAAA CCACTTTGGA AAATAATGAA GGTGGACAAG AGCAAGGACC 660

AAGTGTGGAA GGTCTTAATG TACCAACAAA GGCTACTTTA GAGGTATCCT CTATCATAAA 720

AAAGAAACCA AATCAAGCTA AAAAAGGCCT TGGGGCCAAA AAAGGAAGTT TGGGAGCTCA 780

GAAACTGGCA AACACATGCT TTAATGAAAT TGAAAAACAA GCTCAAGCTG CGGATAAAAT 840

GAAGGAGCAG AAAGACCTGG CCAAGGTGGT ATCTAAAGAA GAATCAATTG TTTCATCATT 900

ACGATTAGCC TATAAGGATC TTGAAATTCA AATGAAGAAA GACGAAAAGA TGAACATTAG 960

TGGCAAAAAA AATGTTGACT CAGACAGACT CGGCATGGGA TTTGGAAATT GCAGAAGTGT 1020

TATTTCACAT TCAGTGACTT CAGATATGCA GACCATAGAG CAGGAATCAC CCATTATGGC 1080

AAAACCAAGA AAAAAGTATA ATGATGACAG TGACGATTCA TATTTTACTT CCAGCTCAAG 1140

TTACTTTGAC GAGCCAGTGG AGTTAAGGAG CAGTTCTTTC TCTAGCTGGG ATGACAGTTC 1200

AGATTCCTAT TGGAAAAAAG AGACCAGCAA AGATACTGAA ACAGTTCTGA AAACCACAGG 1260

CTATTCAGAC AGACCTACTG CTCGCCGCAA GCCAGATTAT GAGCCAGTTG AAAATACAGA 1320

TGAGGCCCAG AAGAAGTTTG GCAATGTCAA GGCCATTTCA TCAGATATGT ATTTTGGAAG 1380

ACAATCCCAG GCTGATTATG AGACCAGGGC CCGCCTAGAG AGGCTGTCGG CAAGTTCCTC 1440

CATAAGCTCG GCTGATCTGT TCGAGGAGCC GAGGAAGCAG CCAGCAGGGA ACTACAGCCT 1500

GTCCAGTGTG CTGCCCAACG CCCCCGACAT GGCGCAGTTC AAGCAGGGAG TGAGATCGGT 1560

TGCTGGAAAA CTCTCCGTCT TTGCTAATGG AGTCGTGACT TCAATTCAGG ATCGCTACGG 1620

TTCTTAATAC TGAAGTCATG ATGTGTATTT CCTGGAGAAA TTCCTCTTTA AATGAACAAG 1680

TAACCACATC TCAGGCGGCA GTGAAGTCCA GATAGTTTTG CAGATTGTTT TGCTACTTTT 1740

TCATATGGTA TATGTTTCTG ATTTTTAATA TTTCTTTTGA GAAATTCTGA GTTCTGATGT 1800

AGGAGCTTTC CTGTGATTTC TGTTTCACGT TCCTTCCTGT CACACCCTCC TTTGGCGTCT 1860

CTGTGTATAT CCTTGCTTTA TTTTCTTGGA ACCTTTGATT TCAACACTGA GGGCCTGGAG 1920

ACCTCGGCTC CTCCTGCTCC TGAACCAGGA GGCTTCATGT GGGGGAGGAG GAGAGGTCTC 1980

CATGTGACAC ATGGGCTCAG GGCTGCCAGA ATCAGCGGAT GCTGGATGGG CCTGCAGAAA 2040

CAACACTCAC CACACACACT TCCTTCAAAA GACCAAAAGT GACTGGTGTC TCGTGTGACA 2100

GATTGCTTCA TTTATGTTTC TACATAGTAA GGTGACTGCC AAATAATATT TGAAGTCATC 2160

TGTCTCTTTG TAAATTATTT TATATGACCT ATAAATTTAA AAATGTTTTT CAGTGAGTGC 2220

TTTTAACAAA CTTAAGCTTC TGCCCTGCCA AGGGAATTAA TGTTATCTTG TGAAAGGTGT 2280

TGCTGTTTGA ATTGATGAGA AATGGAAGAT GAGAACTCCC TAAGAGTTCT CATAATAAAT 2340

CATCTCATCA CAAATCAATA CGGTATACAG AGTTAAAGTG GAATGAGGTA AGAAGATACA 2400

GCTACAGAAA ATAGTTGCGT GTATGGGAGA ACAGTCATTG TAATTGGGTA GTTTTGTTAA 2460

TAAATATTTT TAAATCTTGC TTTTCAGAAA TTACCGAATG TGTATAAACA AATAAAGAAA 2520

AATAATTTAG CTGTGTTTTA GACAGCATTA GAATATATTG TTCAGCACAG TAAAATATAT 2580

TTGAAATTTG ATAAGCCAAA AATGTGGTTT TGAATGAATA TTTTGTGAAT CTTTCTTAAA 2640

AGCTCAAATT TGTAGACTTC TAAATAGAAT AAACACTTGC AGCAGATGGA AAAAAAAAAA 2700

AAAAA 2705

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 516 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Gly Asp Pro Ser Lys Gln Asp Ile Leu Thr Ile Phe Lys Arg Leu
1 5 10 15

Arg Ser Val Pro Thr Asn Lys Val Cys Phe Asp Cys Gly Ala Lys Asn
20 25 30

Pro Ser Trp Ala Ser Ile Thr Tyr Gly Val Phe Leu Cys Ile Asp Cys
35 40 45

Ser Gly Ser His Arg Ser Leu Gly Val His Leu Ser Phe Ile Arg Ser
50 55 60

Thr Glu Leu Asp Ser Asn Trp Ser Trp Phe Gln Leu Arg Cys Met Gln
65 70 75 80

Val Gly Gly Asn Ala Ser Ala Ser Ser Phe Phe His Gln His Gly Cys
85 90 95

Ser Thr Asn Asp Thr Asn Ala Lys Tyr Asn Ser Arg Ala Ala Gln Leu
100 105 110

Tyr Arg Glu Lys Ile Lys Ser Leu Ala Ser Gln Ala Thr Arg Lys His
115 120 125

Gly Thr Asp Leu Trp Leu Asp Ser Cys Val Val Pro Pro Leu Ser Pro
130 135 140

Pro Pro Lys Glu Glu Asp Phe Phe Ala Ser His Val Ser Pro Glu Val
145 150 155 160

Ser Asp Thr Ala Trp Ala Ser Ala Ile Ala Glu Pro Ser Ser Leu Thr
165 170 175

Ser Arg Pro Val Glu Thr Thr Leu Glu Asn Asn Glu Gly Gly Gln Glu
180 185 190

```
Gln Gly Pro Ser Val Glu Gly Leu Asn Val Pro Thr Lys Ala Thr Leu
        195                 200                 205

Glu Val Ser Ser Ile Ile Lys Lys Lys Pro Asn Gln Ala Lys Lys Gly
    210                 215                 220

Leu Gly Ala Lys Lys Gly Ser Leu Gly Ala Gln Lys Leu Ala Asn Thr
225                 230                 235                 240

Cys Phe Asn Glu Ile Glu Lys Gln Ala Gln Ala Ala Asp Lys Met Lys
                245                 250                 255

Glu Gln Lys Asp Leu Ala Lys Val Val Ser Lys Glu Glu Ser Ile Val
            260                 265                 270

Ser Ser Leu Arg Leu Ala Tyr Lys Asp Leu Glu Ile Gln Met Lys Lys
        275                 280                 285

Asp Glu Lys Met Asn Ile Ser Gly Lys Lys Asn Val Asp Ser Asp Arg
    290                 295                 300

Leu Gly Met Gly Phe Gly Asn Cys Arg Ser Val Ile Ser His Ser Val
305                 310                 315                 320

Thr Ser Asp Met Gln Thr Ile Glu Gln Glu Ser Pro Ile Met Ala Lys
                325                 330                 335

Pro Arg Lys Lys Tyr Asn Asp Asp Ser Asp Asp Ser Tyr Phe Thr Ser
            340                 345                 350

Ser Ser Ser Tyr Phe Asp Glu Pro Val Glu Leu Arg Ser Ser Ser Phe
        355                 360                 365

Ser Ser Trp Asp Asp Ser Ser Asp Ser Tyr Trp Lys Lys Glu Thr Ser
    370                 375                 380

Lys Asp Thr Glu Thr Val Leu Lys Thr Thr Gly Tyr Ser Asp Arg Pro
385                 390                 395                 400

Thr Ala Arg Arg Lys Pro Asp Tyr Glu Pro Val Glu Asn Thr Asp Glu
                405                 410                 415

Ala Gln Lys Lys Phe Gly Asn Val Lys Ala Ile Ser Ser Asp Met Tyr
            420                 425                 430

Phe Gly Arg Gln Ser Gln Ala Asp Tyr Glu Thr Arg Ala Arg Leu Glu
        435                 440                 445

Arg Leu Ser Ala Ser Ser Ser Ile Ser Ser Ala Asp Leu Phe Glu Glu
    450                 455                 460

Pro Arg Lys Gln Pro Ala Gly Asn Tyr Ser Leu Ser Ser Val Leu Pro
465                 470                 475                 480

Asn Ala Pro Asp Met Ala Gln Phe Lys Gln Gly Val Arg Ser Val Ala
```

485 490 495

Gly Lys Leu Ser Val Phe Ala Asn Gly Val Val Thr Ser Ile Gln Asp
500 505 510

Arg Tyr Gly Ser
515

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1414 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTTCCACGCC CGAGGGCATC GCGCTGGCCT ACGGCAGCCT CCTGCTCATG GCGCTGCTGC 60

CCATCTTCTT CGGCGCCCTG CGCTCCGTAC GCTGCGCCCG CGGCAAGAAT GCTTCAGACA 120

TGCCTGAAAC AATCACCAGC CGGGATGCCG CCCGCTTCCC CATCATCGCC AGCTGCACAC 180

TCTTGGGGCT CTACCTCTTT TTCAAAATAT TCTCCCAGGA GTACATCAAC CTCCTGCTGT 240

CCATGTATTT CTTCGTGCTG GGAATCCTGG CCCTGTCCCA CACCATCAGC CCCTTCATGA 300

ATAAGTTTTT TCCAGCCAGC TTTCCAAATC GACAGTACCA GCTGCTCTTC ACACAGGGTT 360

CTGGGGAAAA CAAGGAAGAG ATCATCAATT ATGAATTTGA CACCAAGGAC CTGGTGTGCC 420

TGGGCCTGAG CAGCATCGTT GGCGTCTGGT ACCTGCTGAG GAAGCACTGG ATTGCCAACA 480

ACCTTTTTGG CCTGGCCTTC TCCCTTAATG GAGTAGAGCT CCTGCACCTC AACAATGTCA 540

GCACTGGCTG CATCCTGCTG GGCGGACTCT TCATCTACGA TGTCTTCTGG GTATTTGGCA 600

CCAATGTGAT GGTGACAGTG GCCAAGTCCT TCGAGGCACC AATAAAATTG GTGTTTCCCC 660

AGGATCTGCT GGAGAAAGGC CTCGAAGCAA ACAACTTTGC CATGCTGGGA CTTGGAGATG 720

TCGTCATTCC AGGGATCTTC ATTGCCTTGC TGCTGCGCTT TGACATCAGC TTGAAGAAGA 780

ATACCCACAC CTACTTCTAC ACCAGCTTTG CAGCCTACAT CTTCGGCCTG GGCCTTACCA 840

TCTTCATCAT GCACATCTTC AAGCATGCTC AGCCTGCCCT CCTATACCTG GTCCCCGCCT 900

GCATCGGTTT TCCTGTCCTG GTGGCGCTGG CCAAGGGAGA AGTGACAGAG ATGTTCAGTT 960

ATGAGGAGTC AAATCCTAAG GATCCAGCGG CAGTGACAGA ATCCAAAGAG GGAACAGAGG 1020

CATCAGCATC GAAGGGGCTG GAGAAGAAAG AGAAATGATG CAGCTGGTGC CCGAGCCTCT 1080

CAGGGCCAGA CCAGACAGAT GGGGGCTGGG CCCACACAGG CGTGCACCGG TAGAGGGCAC 1140

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TCTGTGGCCT CTGTTTCCTT CTCCCTTTCT TGGCCCTCCT CTGCTCCTCC CCACACCCTG 1260

CAGGCAAAAG AAACCCCCAG CTTCCCCCCT CCCCGGGAGC CAGGTGGGAA AAGTGGGTGT 1320

GATTTTTAGA TTTTGTATTG TGGACTGATT TTGCCTCACA TTAAAAACTC ATCCCATGGC 1380

CAGGGCGGGC CACTGTAAAA AAAAAAAAAA AAAA 1414

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ala Leu Leu Pro Ile Phe Phe Gly Ala Leu Arg Ser Val Arg Cys
1 5 10 15

Ala Arg Gly Lys Asn Ala Ser Asp Met Pro Glu Thr Ile Thr Ser Arg
20 25 30

Asp Ala Ala Arg Phe Pro Ile Ile Ala Ser Cys Thr Leu Leu Gly Leu
35 40 45

Tyr Leu Phe Phe Lys Ile Phe Ser Gln Glu Tyr Ile Asn Leu Leu Leu
50 55 60

Ser Met Tyr Phe Phe Val Leu Gly Ile Leu Ala Leu Ser His Thr Ile
65 70 75 80

Ser Pro Phe Met Asn Lys Phe Phe Pro Ala Ser Phe Pro Asn Arg Gln
85 90 95

Tyr Gln Leu Leu Phe Thr Gln Gly Ser Gly Glu Asn Lys Glu Glu Ile
100 105 110

Ile Asn Tyr Glu Phe Asp Thr Lys Asp Leu Val Cys Leu Gly Leu Ser
115 120 125

```
Ser Ile Val Gly Val Trp Tyr Leu Leu Arg Lys His Trp Ile Ala Asn
    130                 135                 140

Asn Leu Phe Gly Leu Ala Phe Ser Leu Asn Gly Val Glu Leu Leu His
145                 150                 155                 160

Leu Asn Asn Val Ser Thr Gly Cys Ile Leu Leu Gly Gly Leu Phe Ile
                165                 170                 175

Tyr Asp Val Phe Trp Val Phe Gly Thr Asn Val Met Val Thr Val Ala
            180                 185                 190

Lys Ser Phe Glu Ala Pro Ile Lys Leu Val Phe Pro Gln Asp Leu Leu
        195                 200                 205

Glu Lys Gly Leu Glu Ala Asn Asn Phe Ala Met Leu Gly Leu Gly Asp
    210                 215                 220

Val Val Ile Pro Gly Ile Phe Ile Ala Leu Leu Leu Arg Phe Asp Ile
225                 230                 235                 240

Ser Leu Lys Lys Asn Thr His Thr Tyr Phe Tyr Thr Ser Phe Ala Ala
                245                 250                 255

Tyr Ile Phe Gly Leu Gly Leu Thr Ile Phe Ile Met His Ile Phe Lys
            260                 265                 270

His Ala Gln Pro Ala Leu Leu Tyr Leu Val Pro Ala Cys Ile Gly Phe
        275                 280                 285

Pro Val Leu Val Ala Leu Ala Lys Gly Glu Val Thr Glu Met Phe Ser
    290                 295                 300

Tyr Glu Glu Ser Asn Pro Lys Asp Pro Ala Ala Val Thr Glu Ser Lys
305                 310                 315                 320

Glu Gly Thr Glu Ala Ser Ala Ser Lys Gly Leu Glu Lys Lys Glu Lys
                325                 330                 335
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1583 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AGACGAGCCT TTCTTATTTC TTTACTCAAC CTCTTTGATG ACACAGCAAA AACAGACGTG 60

ACTATGCTCT TGTATATAGC AGACAATCTA GCCTGTTTTC CATACCAGAC ACAGGAAGAG 120

CCGTTGTTTA TAATGCATCA TATAGACATT ACACTCTCAG TTTCTGGTAG TAACCTACTG 180

CAGTCATTCA AGGAGTCTAT GGTAAAGGAC AAAAGGAAAG AGAGAAAATC ATCACCTAGT 240

AAGGAAAATG AGTCAAGCGA CAGTGAAGAA GAAGTTTCCA GGCCTCGGAA GTCACGGAAA 300

CGTGTAGATT CAGATTCAGA TTCAGATTCA GAAGACGATA TAAATTCAGT GATGAAATGT 360

TTGCCAGAAA ATTCAGCTCC TTTAATCGAA TTTGCAAATG TGTCCCAGGG TATTTTATTA 420

CTTCTCATGT TAAAACAACA TTTGAAGAAT CTTTGTGGAT TTTCTGATAG TAAAATTCAG 480

AAGTACTCTC CATCTGAATC TGCAAAAGTA TATGATAAAG CGATAAACCG AAAAACAGGA 540

GTTCATTTTC ATCCAAAACA AACACTGGAC TTCCTGCGGA GTGACATGGC TAATTCCAAA 600

ATCACAGAAG AGGTGAAAAG GAGTATAGTA AAACAGTATC TAGATTTCAA ACTTCTCATG 660

GAACATCTGG ACCCTGATGA AGAAGAAGAA GAAGGGGAGG TTTCAGCTAG CACAAATGCT 720

CGGAACAAAG CAATTACCTC ACTGCTTGGA GGAGGCAGCC CTAAAAATAA TACAGCAGCA 780

GAGACAGAAG ATGATGAAAG TGATGGGGAG GATAGAGGAG GAGGCACTTC AGGGTCATTG 840

AGAAGGTCAA AACGAAATTC AGACTCTACG GAGTTGGCAG CACAGATGAA TGAAAGTGTT 900

GACGTCATGG ATGTCATCGC TATTTGCTGT CCAAAGTACA AAGATCGACC ACAAATTGCA 960

AGAGTAGTGC AGAAAACCAG CAGTGGCTTC AGTGTTCAGT GGATGGCAGG CTCCTACAGT 1020

GGCTCCTGGA CTGAGGCTAA GCGCCGTGAT GGCCGCAAAC TGGTGCCTTG GGTAGACACT 1080

ATTAAAGAGT CAGACATTAT TTACAAAAAA ATTGCTCTAA CGAGTGCTAA TAAGCTGACT 1140

AATAAAGTTG TTCAGACTTT ACGATCCCTG TATGCCGCCA AGGATGGGAC TTCCAGCTAA 1200

TGAATTTGTA CATGCAGCCA AATTTACAGG AATTTTTTTA AAAGGCAGAA AAACTTGAAA 1260

TACCAACATT CTGGCAAAAA AAAATCAGTT TTATGAAGAG TAAGTGGAAC CTGGGATGCA 1320

GGAACAAAAG AAGGAAATGT TGGGCAAACA TTTTTGTGGG AGCTCCCTTC GCTGTTGTGC 1380

AGCAGAAACA GATTCTCAGT TCATTTTTAC TCCCACTGTA TTATAGTTTA ACAAAAATTG 1440

TTTATATCTT GGAAAAAAAA ACTTTCTGTT TAAAAAAAAT AAACAAGTGA ATGTTGGAAA 1500

TTAGTCTGTT AATGTTCTTA ATAAAGTGTT CTTGGAGTTT TAAAAAAAAA AAAAAAAAAA 1560

AAAAAAAAAA AAAAAAAAAA AAA 1583

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 378 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Met Leu Leu Tyr Ile Ala Asp Asn Leu Ala Cys Phe Pro Tyr Gln Thr
1               5                  10                  15

Gln Glu Glu Pro Leu Phe Ile Met His His Ile Asp Ile Thr Leu Ser
            20                  25                  30

Val Ser Gly Ser Asn Leu Leu Gln Ser Phe Lys Glu Ser Met Val Lys
        35                  40                  45

Asp Lys Arg Lys Glu Arg Lys Ser Ser Pro Ser Lys Glu Asn Glu Ser
    50                  55                  60

Ser Asp Ser Glu Glu Glu Val Ser Arg Pro Arg Lys Ser Arg Lys Arg
65                  70                  75                  80

Val Asp Ser Asp Ser Asp Ser Asp Ser Glu Asp Asp Ile Asn Ser Val
                85                  90                  95

Met Lys Cys Leu Pro Glu Asn Ser Ala Pro Leu Ile Glu Phe Ala Asn
            100                 105                 110

Val Ser Gln Gly Ile Leu Leu Leu Leu Met Leu Lys Gln His Leu Lys
        115                 120                 125

Asn Leu Cys Gly Phe Ser Asp Ser Lys Ile Gln Lys Tyr Ser Pro Ser
    130                 135                 140

Glu Ser Ala Lys Val Tyr Asp Lys Ala Ile Asn Arg Lys Thr Gly Val
145                 150                 155                 160

His Phe His Pro Lys Gln Thr Leu Asp Phe Leu Arg Ser Asp Met Ala
                165                 170                 175

Asn Ser Lys Ile Thr Glu Glu Val Lys Arg Ser Ile Val Lys Gln Tyr
            180                 185                 190

Leu Asp Phe Lys Leu Leu Met Glu His Leu Asp Pro Asp Glu Glu Glu
        195                 200                 205

Glu Glu Gly Glu Val Ser Ala Ser Thr Asn Ala Arg Asn Lys Ala Ile
    210                 215                 220
```

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Thr Ser Leu Leu Gly Gly Gly Ser Pro Lys Asn Asn Thr Ala Ala Glu
225                 230                 235                 240

Thr Glu Asp Asp Glu Ser Asp Gly Glu Asp Arg Gly Gly Gly Thr Ser
                245                 250                 255

Gly Ser Leu Arg Arg Ser Lys Arg Asn Ser Asp Ser Thr Glu Leu Ala
            260                 265                 270

Ala Gln Met Asn Glu Ser Val Asp Val Met Asp Val Ile Ala Ile Cys
        275                 280                 285

Cys Pro Lys Tyr Lys Asp Arg Pro Gln Ile Ala Arg Val Val Gln Lys
    290                 295                 300

Thr Ser Ser Gly Phe Ser Val Gln Trp Met Ala Gly Ser Tyr Ser Gly
305                 310                 315                 320

Ser Trp Thr Glu Ala Lys Arg Arg Asp Gly Arg Lys Leu Val Pro Trp
                325                 330                 335

Val Asp Thr Ile Lys Glu Ser Asp Ile Ile Tyr Lys Lys Ile Ala Leu
            340                 345                 350

Thr Ser Ala Asn Lys Leu Thr Asn Lys Val Val Gln Thr Leu Arg Ser
        355                 360                 365

Leu Tyr Ala Ala Lys Asp Gly Thr Ser Ser
    370                 375
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2353 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
TCCCGTCGCG CTCAGCATCC TCAATCATCC GCAGGCTGAT GCGGTCCTTC ACGCTCCCGC      60

CCGCGTTGAA GAACTCACAC TTGGCCAAGA GCTCACACTT CAGGCCGAAC TTCTTCCCAA     120

TCTTGTTGAT TCTGACCATA GGGGTGTCCC CGATTTTCTT CAGAATATCT GGCAAGATTT     180

TTGGAGATTT TGCCGGGGCA GTGTGGTGAT GTGGGGACTC GGAGGCAGGC CGGCCCAGCT     240

GCCAGGTGCA CCTGCTCGGA GCATCGGGCC GGATCCACAG GGGCTCCTTG GCTTCCTTAT     300
```

CCTCTGGGGA CCCCTTCTCC AGGCTCCCCT TCGCCGAGTG TGGCCCTGAG CGGTGGGGGC 360

AGCCTGTGGG CCCCACTTCT GCCTGGGGGG TCTCAGAAGG CATGCTGGGA CCGGACAGAT 420

GGTGCTGACA GTTCAGCACC GCTCAAACTC TGTAAGGAGA CGTGACAACA GAATCTGTCA 480

TGGGATCCTG GAATAGAAAA GGGCAGTGAG GAGAAAACTC TGCAAATCTG ACTCAAGCGC 540

GGACTTTGGT TAGGCCTCTT TGGACAGTAC TTTGAGAATT ATGGATCTCC GGATATTAGT 600

AGCAAGGAAG TTTGTAGGAG CAGCAAATTA TCGGGAGAAG ATTCATAGTA CTTTGACTCC 660

ATGTGGGACT TTTCTGTTTG CTGGAAGTGA GGATGGTATA GTGTATGTTT GGAACCCAGA 720

AACAGGAGAA CAAGTAGCCA TGTATTCTGA CTTGCCATTC AAGTCACCCA TTCGAGACAT 780

TTCTTATCAT CCATTTGAAA ATATGGTTGC ATTCTGTGCA TTTGGGCAAA ATGAGCCAAT 840

TCTTCTGTAT ATTTACGATT TCCATGTTGC CCAGCAGGAG GCTGAAATGT TCAAACGCTA 900

CAATGGAACA TTTCCATTAC CTGGAATACA CCAAAGTCAA GATGCCCTAT GTACCTGTCC 960

AAAACTACCC CATCAAGGCT CTTTTCAGAT TGATGAATTT GTCCACACTG AAAGTTCTTC 1020

AACGAAGATG CAGCTAGTAA AACAGAGGCT TGAAACTGTC ACAGAGGTGA TACGTTCCTG 1080

TGCTGCAAAA GTCAACAAAA ATCTCTCATT TACTTCACCA CCAGCAGTTT CCTCACAACA 1140

GTCTAAGTTA AAGCAGTCAA ACATGCTGAC CGCTCAAGAG ATTCTACATC AGTTTGGTTT 1200

CACTCAGACC GGGATTATCA GCATAGAAAG AAAGCCTTGT AACCATCAGG TAGATACAGC 1260

ACCAACGGTA GTGGCTCTTT ATGACTACAC AGCGAATCGA TCAGATGAAC TAACCATCCA 1320

TCGCGGAGAC ATTATCCGAG TGTTTTTCAA AGATAATGAA GACTGGTGGT ATGGCAGCAT 1380

AGGAAAGGGA CAGGAAGGTT ATTTTCCAGC TAATCATGTG GCTAGTGAAA CACTGTATCA 1440

AGAACTGCCT CCTGAGATAA AGGAGCGATC CCCTCCTTTA AGCCCTGAGG AAAAAACTAA 1500

AATAGAAAAA TCTCCAGCTC CTCAAAAGGT AAAATAAAAC AAAACAGCTC ACAGAGACAC 1560

CTCCTTCTTC CCCCTGCTTC TGCCTCCATG AGTAACTACC TATATGACGT GCTGCTGCTG 1620

AGACCAAGGA ATGAGTGAGT AAAGGTGTTT GGAAGTCAAA TATTGGTCCT AGTTAAGTAA 1680

GTGTCCTTTT CAAGTAAGTG GTAAACTTTG TAATGTGGAC CCCCTTCTAA CTTAGGATTC 1740

ATATAATTTG AACACAGGCT AAGCTGCCTC TGCATCATTA AAAAGGATTT GGGTATGCCA 1800

GTGATAGGAA TACACAGTAG AAAAGATGGC AGGGACCATG TTTAACATAC CTAAGACAAA 1860

CTTTCTGAGG ATATCACAGC ATCCATTTCA CATGAACAGA CTTAGCAGAA TTGGCAAGAC 1920

CTGCACATGG CAACATATTA TTCATTTTTC AGGATAACAA AAAATAATTA AAAGTAACAT 1980

TGGCTTAACA CTGGTATATA GTTCAGTATG ACTTCTCTCC CCTCAACCTC TGGAATAGGT 2040

TCAAATTGAT GAGAATTTCT GATTAGAGCC CTTAATGTTG AGTTTTTTGA AAAGTTTTAT 2100

CAAGTTTCAT ATATACCTAT ATTGATGGTA AGTTGCTGGT CTTGCCATGG GCAAAGAGAG 2160

AAAAATGATA YTGAGACCTT GTAAAGAATA GYTGGACATG GAGGCGCACA CCTGTAATCC 2220

CAGCAAYTCA GAAGGCTGAG GCGGGAGGAT TGCTTGAGCC CAGGAGTTCA AGGCTGCAGT 2280

GAGCTACGAT CATGCCACTG TACTCCAGCC TGAGCAACAA AGCATGACCC AATCTCTTAA 2340

AAAAAAAAAA AAA 2353

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 318 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Asp Leu Arg Ile Leu Val Ala Arg Lys Phe Val Gly Ala Ala Asn
1 5 10 15

Tyr Arg Glu Lys Ile His Ser Thr Leu Thr Pro Cys Gly Thr Phe Leu
20 25 30

Phe Ala Gly Ser Glu Asp Gly Ile Val Tyr Val Trp Asn Pro Glu Thr
35 40 45

Gly Glu Gln Val Ala Met Tyr Ser Asp Leu Pro Phe Lys Ser Pro Ile
50 55 60

Arg Asp Ile Ser Tyr His Pro Phe Glu Asn Met Val Ala Phe Cys Ala
65 70 75 80

Phe Gly Gln Asn Glu Pro Ile Leu Leu Tyr Ile Tyr Asp Phe His Val
85 90 95

Ala Gln Gln Glu Ala Glu Met Phe Lys Arg Tyr Asn Gly Thr Phe Pro
100 105 110

Leu Pro Gly Ile His Gln Ser Gln Asp Ala Leu Cys Thr Cys Pro Lys
115 120 125

Leu Pro His Gln Gly Ser Phe Gln Ile Asp Glu Phe Val His Thr Glu
130 135 140

```
Ser Ser Ser Thr Lys Met Gln Leu Val Lys Gln Arg Leu Glu Thr Val
145                 150                 155                 160

Thr Glu Val Ile Arg Ser Cys Ala Ala Lys Val Asn Lys Asn Leu Ser
                165                 170                 175

Phe Thr Ser Pro Pro Ala Val Ser Ser Gln Gln Ser Lys Leu Lys Gln
            180                 185                 190

Ser Asn Met Leu Thr Ala Gln Glu Ile Leu His Gln Phe Gly Phe Thr
        195                 200                 205

Gln Thr Gly Ile Ile Ser Ile Glu Arg Lys Pro Cys Asn His Gln Val
    210                 215                 220

Asp Thr Ala Pro Thr Val Val Ala Leu Tyr Asp Tyr Thr Ala Asn Arg
225                 230                 235                 240

Ser Asp Glu Leu Thr Ile His Arg Gly Asp Ile Ile Arg Val Phe Phe
                245                 250                 255

Lys Asp Asn Glu Asp Trp Trp Tyr Gly Ser Ile Gly Lys Gly Gln Glu
            260                 265                 270

Gly Tyr Phe Pro Ala Asn His Val Ala Ser Glu Thr Leu Tyr Gln Glu
        275                 280                 285

Leu Pro Pro Glu Ile Lys Glu Arg Ser Pro Pro Leu Ser Pro Glu Glu
    290                 295                 300

Lys Thr Lys Ile Glu Lys Ser Pro Ala Pro Gln Lys Val Lys
305                 310                 315
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2567 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
AGCCCACCTA CACACCCAGC TCCCACCCAT GGAGAGCACC CCAGTCCTGT TCCTCCTGCC      60

CTGGACCCTG GCCAACTCTG CCACAAGCTC TACCCTCGGT ACAACAGGCT CTGTCCCCAC     120

ATCTACAGAC CCTGCCCCAT CTGCACACCT AGACTCAGTT CATAAGTCCA CAGACTCTGG     180

CCCTTCAGAA CTGCCAGGCC CCACTCACAC CACTACAGGC TCTACCTATA GTGCCATTAC     240
```

CACTACCCAC AGTGCTCCAA GCCCCCTCAC TCACACTACT ACAGGCTCCA CCCACAAGCC 300

CATAATCTCT ACCCTTACTA CTACAGGCCC TACCCTCAAT ATCATAGGCC CAGTCCAGAC 360

TACCACAAGC CCCACCCACA CTATGCCAAG CCCTACCCAT ACCACAGCAA GCCCCACTCA 420

TACTTCCACA AGCCCCACCC ATACCCCCAC AAGTCCCACC CACAAAACCA GTATGTCACC 480

TCCCACCACT ACAAGTCCTA CCCCCAGTGG TATGGGCCTA GTCCAGACTG CCACAAGTCC 540

CACCCATCCT ACCACAAGCC CCACCCATCC CACCACAAGC CCCATCCTTA TAAATGTAAG 600

CCCTTCCACT TCTCTAGAAC TTGCTACCCT CTCCAGCCCC TCCAAACACT CAGACCCCAC 660

CCTCCCAGGC ACTGACTCCC TTCCCTGTAG TCCCCCAGTC TCCAATTCCT ACACTCAGGC 720

AGACCCTATG GCCCCCAGAA CTCCCCACCC AAGTCCTGCC CATTCCAGTA GGAAACCCCT 780

CACAAGCCCT GCCCCAGATC CCTCAGAGTC TACGGTTCAG AGTCTAAGCC CCACTCCCTC 840

ACCCCCAACC CCTGCACCCC AGCATTCAGA CCTTTGCCTG GCCATGGCTG TCCAGACCCC 900

AGTCCCAACG GCAGCCGGAG GGTCTGGGGA CAGGAGCCTG GAGGAGGCAC TGGGGGCCCT 960

AATGGCTGCC CTGGATGACT ACCGTGGCCA GTTTCCTGAG CTGCAGGGCC TGGAGCAGGA 1020

GGTGACCCGC CTAGAAAGTC TGCTCATGCA GAGACAAGGT CTGACTCGCA GCCGGGCCTC 1080

CAGTCTCAGC ATCACTGTGG AGCATGCCTT GGAGAGCTTC AGCTTCCTCA ATGAAAACGA 1140

AGATGAAGAC AATGATGTTC CTGGGGACAG GCCTCCAAGC AGCCCGGAGG CTGGGGCTGA 1200

GGACAGCATA GACTCACCCA GTGCCCGCCC CCTCAGCACG GGGTGTCCAG CTCTGGATGC 1260

TGCCTTGGTC CGGCACCTGT ACCACTGCAG TCGCCTCCTG CTGAAACTGG GCACATTTGG 1320

GCCCCTGCGC TGCCAGGAGG CATGGGCCCT GGAGCGGCTG CTGCGGGAAG CCCGAGTACT 1380

GGAGGCAGTA TGCGAGTTCA GCAGGCGGTG GGAGATCCCG GCCAGCTCTG CCCAGGAAGT 1440

GGTGCAGTTC TCGGCCTCTC GGCCTGGCTT CCTGACCTTC TGGGACCAGT GCACAGAGAG 1500

ACTCAGCTGC TTCCTCTGCC CGGTGGAGCG GGTGCTTCTC ACCTTCTGCA ACCAGTATGG 1560

TGCCCGCCTC TCCCTGCGCC AGCCAGGCTT GGCTGAGGCT GTGTGTGTGA AGTTCCTGGA 1620

GGATGCCCTG GGGCAGAAGC TGCCCAGAAG GCCCCAGCCA GGGCCTGGAG AGCAGCTCAC 1680

AGTCTTCCAG TTCTGGAGTT TTGTGGAAAC CTTGGACAGC CCCACCATGG AGGCCTACGT 1740

GACTGAGACC GCTGAGGAGG TGCTACTGGT GCGGAATCTG AACTCGGATG ATCAGGCTGT 1800

TGTGCTGAAG GCCCTGAGAT TGGCGCCCGA GGGGCGTCTG CGAAGGGACG GGCTGCGGGC 1860

CCTCAGCTCC CTGCTCGTCC ATGGCAACAA CAAGGTCATG GCTGCTGTCA GCACCCAGCT 1920

CCGGAGCCTG TCACTGGGCC CTACCTTCCG GGAGAGGGCC CTCCTGTGCT TCCTGGACCA 1980

GCTGGAGGAT GAGGACGTGC AGACTCGAGT GGCTGGCTGC CTGGCCCTAG GCTGCATCAA 2040

GGCTCCCGAG GGCATTGAGC CCCTGGTGTA CCTCTGCCAA ACTGACACAG AAGCTGTGAG 2100

GGAAGCTGCC CGGCAAAGCC TACAGCAGTG TGGAGAAGAG GGACAGTCTG CCCATCGACG 2160

GCTGGAGGAG TCCCTGGACG CCCTGCCCCG CATCTTTGGG CCTGGCAGCA TGGCCAGCAC 2220

AGCATTCTAA ACTATTCACC CATGGGTTCC TGGTGCCCCT TTCCCCCCAC TTTCAGGGCT 2280

CACCAGGCAC TGGCAGGGAG GGTAAGGGCT GGCTCCAGAT ACCCCTCCCC CACAGATTCC 2340

TAGCAATGAA AATCTAATAT ATTCTTCTGT TGCCCCTGGG GTTGGAGAGT CAGTGCCTGC 2400

AGTCAAGTGC CTCCCAGCCT CGGCTCAGCA CATCCCTTGC CACAAATCAG TGTCTGGGGC 2460

TTGGCCACCC TGCCGCTGCC CAGCCACATC CCTTGGTTTT GTATTTTATT TACAGAGTTT 2520

TACAGAAAAT AAAAAAGCAA AATGTCTTTC CTAAAAAAAA AAAAAAA 2567

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 733 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Glu Ser Thr Pro Val Leu Phe Leu Leu Pro Trp Thr Leu Ala Asn
1 5 10 15

Ser Ala Thr Ser Ser Thr Leu Gly Thr Thr Gly Ser Val Pro Thr Ser
20 25 30

Thr Asp Pro Ala Pro Ser Ala His Leu Asp Ser Val His Lys Ser Thr
35 40 45

Asp Ser Gly Pro Ser Glu Leu Pro Gly Pro Thr His Thr Thr Thr Gly
50 55 60

Ser Thr Tyr Ser Ala Ile Thr Thr Thr His Ser Ala Pro Ser Pro Leu
65 70 75 80

Thr His Thr Thr Thr Gly Ser Thr His Lys Pro Ile Ile Ser Thr Leu
85 90 95

```
Thr Thr Thr Gly Pro Thr Leu Asn Ile Ile Gly Pro Val Gln Thr Thr
            100                 105                 110

Thr Ser Pro Thr His Thr Met Pro Ser Pro Thr His Thr Thr Ala Ser
        115                 120                 125

Pro Thr His Thr Ser Thr Ser Pro Thr His Thr Pro Thr Ser Pro Thr
    130                 135                 140

His Lys Thr Ser Met Ser Pro Pro Thr Thr Thr Ser Pro Thr Pro Ser
145                 150                 155                 160

Gly Met Gly Leu Val Gln Thr Ala Thr Ser Pro Thr His Pro Thr Thr
                165                 170                 175

Ser Pro Thr His Pro Thr Thr Ser Pro Ile Leu Ile Asn Val Ser Pro
            180                 185                 190

Ser Thr Ser Leu Glu Leu Ala Thr Leu Ser Ser Pro Ser Lys His Ser
        195                 200                 205

Asp Pro Thr Leu Pro Gly Thr Asp Ser Leu Pro Cys Ser Pro Pro Val
    210                 215                 220

Ser Asn Ser Tyr Thr Gln Ala Asp Pro Met Ala Pro Arg Thr Pro His
225                 230                 235                 240

Pro Ser Pro Ala His Ser Ser Arg Lys Pro Leu Thr Ser Pro Ala Pro
                245                 250                 255

Asp Pro Ser Glu Ser Thr Val Gln Ser Leu Ser Pro Thr Pro Ser Pro
            260                 265                 270

Pro Thr Pro Ala Pro Gln His Ser Asp Leu Cys Leu Ala Met Ala Val
        275                 280                 285

Gln Thr Pro Val Pro Thr Ala Ala Gly Gly Ser Gly Asp Arg Ser Leu
    290                 295                 300

Glu Glu Ala Leu Gly Ala Leu Met Ala Ala Leu Asp Asp Tyr Arg Gly
305                 310                 315                 320

Gln Phe Pro Glu Leu Gln Gly Leu Glu Gln Glu Val Thr Arg Leu Glu
                325                 330                 335

Ser Leu Leu Met Gln Arg Gln Gly Leu Thr Arg Ser Arg Ala Ser Ser
            340                 345                 350

Leu Ser Ile Thr Val Glu His Ala Leu Glu Ser Phe Ser Phe Leu Asn
        355                 360                 365

Glu Asn Glu Asp Glu Asp Asn Asp Val Pro Gly Asp Arg Pro Pro Ser
    370                 375                 380

Ser Pro Glu Ala Gly Ala Glu Asp Ser Ile Asp Ser Pro Ser Ala Arg
```

```
385                 390                 395                 400

Pro Leu Ser Thr Gly Cys Pro Ala Leu Asp Ala Ala Leu Val Arg His
                405                 410                 415

Leu Tyr His Cys Ser Arg Leu Leu Leu Lys Leu Gly Thr Phe Gly Pro
            420                 425                 430

Leu Arg Cys Gln Glu Ala Trp Ala Leu Glu Arg Leu Leu Arg Glu Ala
        435                 440                 445

Arg Val Leu Glu Ala Val Cys Glu Phe Ser Arg Arg Trp Glu Ile Pro
    450                 455                 460

Ala Ser Ser Ala Gln Glu Val Val Gln Phe Ser Ala Ser Arg Pro Gly
465                 470                 475                 480

Phe Leu Thr Phe Trp Asp Gln Cys Thr Glu Arg Leu Ser Cys Phe Leu
                485                 490                 495

Cys Pro Val Glu Arg Val Leu Leu Thr Phe Cys Asn Gln Tyr Gly Ala
            500                 505                 510

Arg Leu Ser Leu Arg Gln Pro Gly Leu Ala Glu Ala Val Cys Val Lys
        515                 520                 525

Phe Leu Glu Asp Ala Leu Gly Gln Lys Leu Pro Arg Arg Pro Gln Pro
    530                 535                 540

Gly Pro Gly Glu Gln Leu Thr Val Phe Gln Phe Trp Ser Phe Val Glu
545                 550                 555                 560

Thr Leu Asp Ser Pro Thr Met Glu Ala Tyr Val Thr Glu Thr Ala Glu
                565                 570                 575

Glu Val Leu Leu Val Arg Asn Leu Asn Ser Asp Asp Gln Ala Val Val
            580                 585                 590

Leu Lys Ala Leu Arg Leu Ala Pro Glu Gly Arg Leu Arg Arg Asp Gly
        595                 600                 605

Leu Arg Ala Leu Ser Ser Leu Leu Val His Gly Asn Asn Lys Val Met
    610                 615                 620

Ala Ala Val Ser Thr Gln Leu Arg Ser Leu Ser Leu Gly Pro Thr Phe
625                 630                 635                 640

Arg Glu Arg Ala Leu Leu Cys Phe Leu Asp Gln Leu Glu Asp Glu Asp
                645                 650                 655

Val Gln Thr Arg Val Ala Gly Cys Leu Ala Leu Gly Cys Ile Lys Ala
            660                 665                 670

Pro Glu Gly Ile Glu Pro Leu Val Tyr Leu Cys Gln Thr Asp Thr Glu
        675                 680                 685
```

Ala Val Arg Glu Ala Ala Arg Gln Ser Leu Gln Gln Cys Gly Glu Glu
690 695 700

Gly Gln Ser Ala His Arg Arg Leu Glu Glu Ser Leu Asp Ala Leu Pro
705 710 715 720

Arg Ile Phe Gly Pro Gly Ser Met Ala Ser Thr Ala Phe
725 730

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2501 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GGCAGTCAAA GCACTGATGA TGATAAAATC GTTCAGTACC ATTGGGAAGA ACTTAAGGGG 60

CCTCTAAGAG AAGAGAAGAT TTCTGAAGAT ACAGCCATAT TAAAACTAAG TAAACTCGTC 120

CCTGGGAACT ACACTTTCAG CTTGACTGTA GTAGACTCTG ATGGAGCTAC CAACTCTACT 180

ACTGCAAACC TGACAGTGAA CAAAGCTGTG GATTACCCCC CTGTGGCCAA CGCAGGCCCC 240

AACCAAGTGA TCACCCTGCC CCAAAACTCC ATCACCCTCT TTGGGAACCA GAGCACTGAT 300

GATCATGGCA TCACCAGCTA TGAGTGGTCA CTCAGCCCAA GCAGCAAAGG GAAAGTGGTG 360

GAGATGCAGG GTGTTAGAAC ACCAACCTTA CAGCTCTCTG CGATGCAAGA AGGAGACTAC 420

ACTTACCAGC TCACAGTGAC TGACACAATA GGACAGCAGG CCACTGCTCA AGTGACTGTT 480

ATTGTGCAAC CTGAAAACAA TAAGCCTCCT CAGGCAGATG CAGGCCCAGA TAAAGAGCTG 540

ACCCTTCCTG TGGATAGCAC AACCCTGGAT GGCAGCAAGA GCTCAGATGA TCAGAAAATT 600

ATCTCATATC TCTGGGAAAA AACACAGGGA CCTGATGGGG TGCAGCTCGA GAATGCTAAC 660

AGCAGTGTTG CTACTGTGAC TGGGCTGCAA GTGGGGACCT ATGTGTTCAC CTTGACTGTC 720

AAAGATGAGA GGAACCTGCA AAGCCAGAGC TCTGTGAATG TCATTGTCAA AGAAGAATAA 780

ACAAACCACC TATAGCCAAG ATAACTGGGA ATGTGGTGAT TACCCTACCC ACGAGCACAG 840

CAGAGCTGGA TGGCTCTAAG TCCTCAGATG ACAAGGGAAT AGTCAGCTAC CTCTGGACTC 900

GAGATGAGGG GAGCCCAGCA GCAGGGGAGG TGTTAAATCA CTCTGACCAT CACCCTATCC 960

TTTTTCTTTC AAACCTGGTT GAGGGAACCT ACACTTTTCA CCTGAAAGTG ACCGATGCAA 1020

AGGGTGAGAG TGACACAGAC CGGACCACTG TGGAGGTGAA ACCTGATCCC AGGAAAAACA 1080

ACCTGGTGGA GATCATCTTG GATATCAACG TCAGTCAGCT AACTGAGAGG CTGAAGGGGA 1140

TGTTCATCCG CCAGATTGGG GTCCTCCTGG GGGTGCTGGA TTCCGACATC ATTGTGCAAA 1200

AGATTCAGCC GTACACGGAG CAGAGCACCA AAATGGTATT TTTTGTTCAA AACGAGCCTC 1260

CCCACCAGAT CTTCAAAGGC CATGAGGTGG CAGCGATGCT CAAGAGTGAG CTGCGGAAGC 1320

AAAAGGCAGA CTTTTTGATA TTCAGAGCCT TGGAAGTCAA CACTGTCACA TGTCAGCTGA 1380

ACTGTTCCGA CCATGGCTAC TGTGACTCGT TCACCAAACG CTGTATCTGT GACCCTTTTT 1440

GGATGGAGAA TTTCATCAAG GTGCAGCTGA GGGATGGAGA CAGCAACTGT GAGTGGAGCG 1500

TGTTATATGT TATCATTGCT ACCTTTGTCA TTGTTGTTGC CTTGGGAATC CTGTCTTGGA 1560

CTGTGATCTG TTGTTGTAAG AGGCAAAAAG GAAAACCCAA GAGGAAAAGC AAGTACAAGA 1620

TCTGGATGCC ACGGATCAGG AAAGCTTGGA GCTGAAGCCA ACCTCCCGAG CAGGCATCAA 1680

ACAGAAAGGC CTTTTGCTAA GTAGCAGCCT GATGCACTCC GAGTCAGAGC TGGACAGCGA 1740

TGATGCCATC TTTACATGGC CAGACCGAGA GAAGGGCAAA CTCCTGCATG GTCAGAATGG 1800

CTCTGTACCC AACGGGCAGA CCCCTCTGAA GGCCAGGAGC CCGCGGGAGG AGATCCTGTA 1860

GCCACCTGGT CTGTCTCCTC AGGGCAGGGC CCAGCACACT GCCCGGCCAG TCCTCCTACC 1920

TCCCGAGTCT GCGGGCAGCT GCTGTCCCAG CATCTGCTGG TCATTTCGCC CTGACAGTCC 1980

CAACCAGAAC CCCTGGGACT TGAATCCAGA GACGTCCTTC AGGAACCCCT CAACGAAGCT 2040

GTGAATGAAG AGGTTTCCTC TTTAAACCTG TCTGGTGGGC CCCCAGATAT CCTCACCTCA 2100

GGGCCTCCTT TTTTTGCAAA CTCCTCCCCT CCCCCGAGGG CAGACCCAGC CAGCTGCTAA 2160

GCTCTGCAGC TCCCCAGTGG ACAGTGTCAT TGTGCCCAGA GTGCTGCAAG GTGAGGCCTG 2220

CTGTGCTGCC CGCACACCTG AGTGCAAAAC CAAGCACTGT GGGCATGGTG TTTCCCTCTC 2280

TGGGGTAGAG TACGCCCTCT CGCTGGGCAA AGAGGAAGTG GCACCCCTCC CCTCACCACA 2340

GATGCTGAGA TGGTAGCATA GAAATGATGG CCGGGCGCGG TGGCTMACGC CTGTAATCCC 2400

AGCACTTTGG GAGGCCGAGG CGGGCGGATC ATGAGGTCAG GAGATCAAGA CCACCCTGGC 2460

TAACACGGTG AAACCCCATC TCTACTAAAA AAAAAAAAAA A 2501

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 138 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Met Gln Gly Val Arg Thr Pro Thr Leu Gln Leu Ser Ala Met Gln Glu
1               5                  10                  15

Gly Asp Tyr Thr Tyr Gln Leu Thr Val Thr Asp Thr Ile Gly Gln Gln
            20                  25                  30

Ala Thr Ala Gln Val Thr Val Ile Val Gln Pro Glu Asn Asn Lys Pro
        35                  40                  45

Pro Gln Ala Asp Ala Gly Pro Asp Lys Glu Leu Thr Leu Pro Val Asp
    50                  55                  60

Ser Thr Thr Leu Asp Gly Ser Lys Ser Ser Asp Asp Gln Lys Ile Ile
65                  70                  75                  80

Ser Tyr Leu Trp Glu Lys Thr Gln Gly Pro Asp Gly Val Gln Leu Glu
                85                  90                  95

Asn Ala Asn Ser Ser Val Ala Thr Val Thr Gly Leu Gln Val Gly Thr
            100                 105                 110

Tyr Val Phe Thr Leu Thr Val Lys Asp Glu Arg Asn Leu Gln Ser Gln
        115                 120                 125

Ser Ser Val Asn Val Ile Val Lys Glu Glu
    130                 135
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1820 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
GGCAGCAGCA GAGGGAGAGC TCGGGGCTTG GAGGGGAAAC AGCGGAAGAC CTAAGATTAT      60
```

CGGGAGGGCA GCAGAGGCAG AGAACGAGGA CAGGACCCTT GGCCGTCTTC TTCCAGGGAA 120

CGAGAGGTCA CAGCCTCGCT CTCCGCTTAG GCTTCTGGCG CCCCAGCTTA AAGCCGAGGC 180

TGCGGCTGAC AAAGGGCTCG CGCCGGTGCC GCCGCCCTTC TCATCCGGGC ATTCGGGTCC 240

CTGCGGAGAG GGAGGGGGAA GGGCAGAGGG GGAGGGGAAG GAGCCSGAGG GGCSCACACT 300

TGGAGCTGAA GCCCTCTCCA GGGCTCCGGG CCGGTGCCCC AACGGACAGA GGTCGAGGAG 360

GACCCGCAGA GGTGGCAGCG GCCGGGGGCA GGAGGATGGT GCAGAAGGAG AGTCAAGCGA 420

CGTTGGAGGA GCGGGAGAGC GAGCTCAGTT CCAACCCTGC CGCCTCTGCG GGGGCATCGC 480

TGGAGCCGCC GGCAGCTCCG GCACCCGGAG AAGACAACCC CGCCGGGGCT GGGGGAGCGG 540

CGGTGGCCGG GGCTGCAGGA GGGGCTCGGC GGTTTCCTCT GCGGTGTGGT GGAAGGATTT 600

TATGGAAGAC CTTGGGTTAT GGAACAGAGA AAAGAACTCT TTAGAAGGCT CCAGAAATGG 660

GAATTAAATA CATACTTGTA TGCCCCAAAA GATGACTACA AACATAGGAT GTTTTGGCGA 720

GAGATGTATT CAGTGGAGGA AGCTGAGCAA CTTATGACTC TCATCTCTGC TGCACGAGAA 780

TATGAGATAG AGTTCATCTA TGCGATCTCA CCTGGATTGG ATATCACTTT TTCTAACCCC 840

AAGGAAGTAT CCACATTGAA ACGTAAATTG GACCAGGTTT CTCAGTTTGG GTGCAGATCA 900

TTTGCTTTGC TTTTTGATGA TATAGACCAT AATATGTGTG CAGCAGACAA AGAGGTATTC 960

AGTTCTTTTG CTCATGCCCA AGTCTCCATC ACAAATGAAA TCTATCAGTA CCTAGGAGAG 1020

CCAGAAACTT TCCTCTTCTG TCCCACAGAA TACTGTGGCA CTTTCTGTTA TCCAAATGTG 1080

TCTCAGTCTC CATATTTAAG GACTGTGGGT GAAAAGCTTC TACCTGGAAT TGAAGTGCTT 1140

TGGACAGGTC CCAAAGTTGT TTCTAAAGAA ATTCCAGTAG AGTCCATCGA AGAGGTTTCT 1200

AAGATTATTA AGAGAGCTCC AGTAATCTGG GATAACATTC ATGCTAATGA TTATGATCAG 1260

AAGAGACTGT TTCTGGGCCC GTACAAAGGA AGATCCACAG AACTCATCCC ACGGTTAAAA 1320

GGAGTCCTCA CTAATCCAAA TTGTGAATTT GAAGCCAACT ACGTTGCTAT CCACACCCTT 1380

GCCACCTGGT ACAAATCAAA CATGAATGGG AGTGAGAAAA GATGTAGTGA TGACTGACAG 1440

TGAAGATAGT ACTGTGTCCA TCCAGATAAA ATTAGAAAAT GAAGGCAGTG ATGAAGATAT 1500

TGAAACTGAT GTACTCTATA GTCCACAGAT GGCTCTAAAG CTAGCATTAA CAGAATGGTT 1560

GCAAGAGTTT GGTGTGCYTC ATCAATACAG CAGTAGGCAA GTTGCACACA GTGGAGCTAA 1620

AGCAAGTGTA GTTGATGGGA CTCCTTTAGT TGCAGCACCC TCTTTAAATG CCACAACCGT 1680

AGTAACAACA GTTTATCAGG AGCCCATTAT GAGCCAGGGA GCAGCCTTGA GTGGTGAGCC 1740

TACTACTCTG ACCAAGGAAG AAGAAAAGAA ACAGCCTGAT GAAGAACCCA TGGACATGGT 1800

GGTGGAAAAA AAAAAAAAAA 1820

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 272 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Glu Gln Arg Lys Glu Leu Phe Arg Arg Leu Gln Lys Trp Glu Leu
1 5 10 15

Asn Thr Tyr Leu Tyr Ala Pro Lys Asp Asp Tyr Lys His Arg Met Phe
20 25 30

Trp Arg Glu Met Tyr Ser Val Glu Glu Ala Glu Gln Leu Met Thr Leu
35 40 45

Ile Ser Ala Ala Arg Glu Tyr Glu Ile Glu Phe Ile Tyr Ala Ile Ser
50 55 60

Pro Gly Leu Asp Ile Thr Phe Ser Asn Pro Lys Glu Val Ser Thr Leu
65 70 75 80

Lys Arg Lys Leu Asp Gln Val Ser Gln Phe Gly Cys Arg Ser Phe Ala
85 90 95

Leu Leu Phe Asp Asp Ile Asp His Asn Met Cys Ala Ala Asp Lys Glu
100 105 110

Val Phe Ser Ser Phe Ala His Ala Gln Val Ser Ile Thr Asn Glu Ile
115 120 125

Tyr Gln Tyr Leu Gly Glu Pro Glu Thr Phe Leu Phe Cys Pro Thr Glu
130 135 140

Tyr Cys Gly Thr Phe Cys Tyr Pro Asn Val Ser Gln Ser Pro Tyr Leu
145 150 155 160

Arg Thr Val Gly Glu Lys Leu Leu Pro Gly Ile Glu Val Leu Trp Thr
165 170 175

Gly Pro Lys Val Val Ser Lys Glu Ile Pro Val Glu Ser Ile Glu Glu
180 185 190

Val Ser Lys Ile Ile Lys Arg Ala Pro Val Ile Trp Asp Asn Ile His
195 200 205

Ala Asn Asp Tyr Asp Gln Lys Arg Leu Phe Leu Gly Pro Tyr Lys Gly
210 215 220

Arg Ser Thr Glu Leu Ile Pro Arg Leu Lys Gly Val Leu Thr Asn Pro
225 230 235 240

Asn Cys Glu Phe Glu Ala Asn Tyr Val Ala Ile His Thr Leu Ala Thr
245 250 255

Trp Tyr Lys Ser Asn Met Asn Gly Ser Glu Lys Arg Cys Ser Asp Asp
260 265 270

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2405 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TATCCATTAC GTCGACTAAT ACGTACATAA GAATTCAATC GGGAGACAAT GTAATAACCC 60

AAACACTGGG TATTCATATT TGACACATGG GCAAACTTGC CAGTGGAATG GAATTGTGAC 120

CTGACAGAGA AGGGAAGGCA GGCTGACGAA GGTGATCGAA TGGGAGAACA GTGCTGTGGT 180

GATCATGAGA ATGAGGCTTT TCTGTAGCAT GTAAACCAAA CCGGACCCTT GGCAGTTCGT 240

CGTCCCTCAG TTCTCCAGAT GCTATTTTTT GCAGGTTCTA CCAAGTGCTT GTTGATTACC 300

CTAGTTGTAA TTATCTAGGG AAGAGATGAA TGTAAGTGAG AGTGCAGAGC ACTGGGGAGG 360

GTGACAGTGA AATGCAATTA GAGGCAGCAA GAGAGTCCTA GTCTGTTCTC ACATAACCGG 420

ACTTGAACGC TCCAGTGCGA GCAGAGTGCT GGGGGTGGAT TCCACTGCCG AACCACGGCA 480

GCTTTGCTTT ACTCTTCAGC ATGGGGGTGG TAACTAGCTG CACAGCAAGT TATGAAATGG 540

AAAGCAAGCT TAACAGCTGT AATCTCATCG GATACCCTGG AGCAAATGCC TTGGGATTGC 600

CTGAAGTGAA GTGTTTAGCA TCCACCAAAT AGTTGAGTTT CTAAGATGGG CCATGCGGGA 660

TCCCTGCCAC ACGGGTGTGG GGGCAGCGCG CTCCTCCCTG CCTCGGCTGC TGTGTGTCTT 720

AGTCTTCATG TTTCCCCTTG GCGTCACCTC TGGTCCTGTC CATCTTGTGC ACATGTGTCC 780

CTGAGGGCGA GTCACACCTG TGTCTTGAGT CTGCTGTAAG GTGTTCAGTC TACCTCAAGG 840

GGTCATCATG GTAAGCTCTA TCCCACGGCA TCCTCCGTCC ATCACCACAC ACACTGGAAT 900

GTATCCCCCC CGCCCTGCCC CTTCGATAAC CTCCTGACCT TGTCTTTCCT ATAATCACCA 960

CAAACTCCTA GTGCAAATTG GATGCTGCTT TAAATGTGAA AACAATTGTT CAAAAGCTAT 1020

AAAACCTGAA TGAAAGCTGA AGCTGAATTT ATAAGCCTTG TTGCATATGA GCCAAAAGTG 1080

CAAAAAGCTC TATATAATGA ACTAACCTGC CACTCGTATA AATATAAATA TATATAAATA 1140

TATTAAAATC AGACTGTTCT ACAAAATTGT GTATTTGTAT TTTTGTGTAC GTACAATTTT 1200

CTGCTAAGCA GAAGGAGGAT GTAGTATAGG ATGCTGTGAG AAGAGATTTG GTTTAATCCT 1260

ATTTCTTTGT TACTTATTTT TGTTAACATC AGATGCCTGT CTTTGTCTTA TATGTGTATG 1320

ACACTGTTTG GAAAGCTGCA GTATCTCTCT TCCTGAGGTC CAGAGGCCAT TAAAGAATAA 1380

ACATGGGGCT TAGAGGTGTC TTGGCCACCA AACACAGGTA AGCCAACAGA GTTCGGCTCC 1440

CGTACGTGGT GTGGTGGACC TGGGGCCTGG AGCCACTTGT ACTCCTGGGG TGGGACTGAG 1500

GGAGGGAAAG GGCTCCCCCA CTTCAGGCTG GTCACTGTAT GTTGACTTCC CTCTGGGAAG 1560

CAAAATTCCA CTTGTAAAAA TCAGCTTCCA AGACAAAAGA TGATCCGATG TCACTTCTGG 1620

GTCACCAGGA AGGGACACAG GATCTCTCTG AACTTTGGAA CAGACCCTCA TATTCTGGGG 1680

CCAGAAGTTT GCCCAGAAAG CAGCAGGTGG CTCTGCCTGG CTGTAGAGCC CAGCTCATTG 1740

GCTGTCCCTG GGCTTGGTCT CCCTCTTCCG AGTAGTTGCT GCCTTTCTTC AGATCAGGTT 1800

ACCACAATGC CTCCCCGCTG CTGACGCTTC ATCCCCCACA CCTCCAGCCC CAGTTACCTG 1860

GAGCTTCTCA GAACCCACTT TGCCGGTGCT AAAACACAAG AGGGGGTGAA AGTGGCTGCC 1920

AGTAATGGCC AGAAACCAAC CACCAGAGGC CAGGCTGAAA GACAAGCTCC GGGTGTCCAG 1980

GGGCTGACGG GCCAACCATG TGGCAGGTCC CAGGCCCCAC CCACTGCGCC ATCCGCCTCT 2040

GAGCTCCACA GTGGTCCCAC TAATGGGAAC CTCCTCTAGG GAGAGTGATA CTGCACCTTC 2100

ACCCGTAGGA CTCATATTTA TAACAATGTG TAATGGCTGT AGCAAAAAGC CCTTGTTTCT 2160

AGATGTAAAT GGTCAAAGAA ACAAGCGCTC TATTGTTTTG AATAAAATAG TTCAAATGAG 2220

TCCTGTATCA TTGTATCTCC TATTCTGGAT TAGTGCCTTT TGGACAGTAG ACTGTTCTGT 2280

AATTAAAATG TAGTATACTG CTTTTTTGTA CAGTTTTGTT TTAATAAAAC TTTTTTTTAA 2340

TTTGTGTTTA TTTTAGTATT GTACCTATTA GAGAATAAAA TGTATAACTG AAAAAAAAAA 2400

AAAAA 2405

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Gly Thr Ser Ser Arg Glu Ser Asp Thr Ala Pro Ser Pro Val Gly
1 5 10 15

Leu Ile Phe Ile Thr Met Cys Asn Gly Cys Ser Lys Lys Pro Leu Phe
20 25 30

Leu Asp Val Asn Gly Gln Arg Asn Lys Arg Ser Ile Val Leu Asn Lys
35 40 45

Ile Val Gln Met Ser Pro Val Ser Leu Tyr Leu Leu Phe Trp Ile Ser
50 55 60

Ala Phe Trp Thr Val Asp Cys Ser Val Ile Lys Met
65 70 75

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CNAGCAGCAGA TACAGCAGTA AGGAAGGC 29

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GNGCTCTCCTT AATCGCCGTC TCAAACAT 29

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CNTTGGCCAGG TCTTCCTGCT CCTTCATT 29

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ANGCTGCAAAG CTGGTGTAGA AGTAGGTG 29

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

ANTTAGCCATG TCACTCCGCA GGAAGTCC 29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TNTAGTCATAA AGAGCCACTA CCGTTGGT 29

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TNGTATGGGTA GGGCTTGGCA TAGTGTGG 29

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

TNTCAGGTTTG CAGTAGTAGA GTTGGTAG 29

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

CNTCTTCGATG GACTCTACTG GAATTTCT 29

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TNAGCCTGGCC TCTGGTGGTT GGTTTCTG 29

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Thr Leu Lys Leu Cys Ser Pro Pro Lys Asp His Glu Val Leu Gly Val
1               5                  10                  15

Ile Gln Arg Phe Leu Lys Leu Arg Ser Pro Trp Lys Ala Leu Ile Thr
            20                  25                  30

Thr Ile Leu Lys Pro Gln Leu Phe Glu Pro Arg Pro Arg Leu Thr Val
        35                  40                  45

Leu Thr Phe Pro Ser Ser His Glu Gly Glu Ser Phe Pro Leu Ala Trp
    50                  55                  60

Asn Ala Lys Ile Thr Asp Leu Lys Gln Lys Val Glu Asn Leu Phe Asn
65                  70                  75                  80

Glu Lys Cys Gly Glu Ala Leu Gly Leu Lys Gln Ala Val Lys Val Pro
                85                  90                  95

Phe Ala Leu Phe Glu Ser Phe Pro Glu Asp Phe Tyr Val Glu Gly Leu
            100                 105                 110

Pro Glu Gly Val Pro Phe Arg Arg Pro Ser Thr Phe Gly Ile Pro Arg
        115                 120                 125

Leu Glu Lys Ile Leu Arg Asn Lys Ala Lys Ile Lys Phe Ile Ile Lys
    130                 135                 140

Lys Pro Glu Met Phe Glu Thr Ala Ile Lys Glu Ser Thr Ser Ser Lys
145                 150                 155                 160

Ser Pro Pro Arg Lys Ile Asn Ser Ser Pro Asn Val Asn Thr Thr Ala
                165                 170                 175

Ser Gly Val Glu Asp Leu Asn Ile Ile Gln Val Thr Ile Pro Asp Asp
            180                 185                 190

Asp Asn Glu Arg Leu Ser Lys Val Glu Lys Ala Arg Gln Leu Arg Glu
        195                 200                 205

Gln Val Asn Asp Leu Phe Ser Arg Lys Phe Gly Glu Ala Ile Gly Met
    210                 215                 220

Gly Phe Pro Val Lys Val Pro Tyr Arg Lys Ile Thr Ile Asn Pro Gly
225                 230                 235                 240

Cys Val Val Val Asp Gly Met Pro Pro Gly Val Ser Phe Lys Ala Pro
                245                 250                 255

Ser Tyr Leu Glu Ile Ser Ser Met Arg Arg Ile Leu Asp Ser Ala Glu
            260                 265                 270
```

```
Phe Ile Lys Phe Thr Val Ile Arg Pro Phe Pro Gly Leu Val Ile Asn
        275                 280                 285

Asn Gln Leu Val Asp Gln Ser Glu Ser Lys Gly Pro Val Ile Gln Glu
    290                 295                 300

Ser Ala Glu Pro Ser Gln Leu Glu Val Pro Ala Thr Glu Glu Ile Lys
305                 310                 315                 320

Glu Thr Asp Gly Ser Ser Gln Ile Lys Gln Glu Pro Asp Pro Thr Trp
                325                 330                 335
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

ANCTTGGCCA GGTCTTCCTG CTCCTTCAT 29

What is claimed is:

1. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 521 to nucleotide 1111;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 536 to nucleotide 817;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ax318_3 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone ax318_3 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 93 to amino acid 102 of SEQ ID NO:2;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

2. The polynucleotide of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with the polynucleotide of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein encoded by the polynucleotide of claim 2, which process comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying said protein from the culture.

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 4 to amino acid 99;

(c) fragments of the amino acid sequence of SEQ ID NO:2 comprising the amino acid sequence from amino acid 93 to amino acid 102 of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone ax318_3 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

9. The protein of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

10. The protein of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 4 to amino acid 99.

11. A composition comprising the protein of claim 8 and a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

14. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 61 to nucleotide 864;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 826 to nucleotide 1386;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bg140_1 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bg140_1 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 129 to amino acid 138 of SEQ ID NO:4;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

15. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:31;

(c) the amino acid sequence of SEQ ID NO:31 from amino acid 148 to amino acid 249;

(d) fragments of the amino acid sequence of SEQ ID NO:4 comprising the amino acid sequence from amino acid 129 to amino acid 138 of SEQ ID NO:4;

(e) fragments of the amino acid sequence of SEQ ID NO:31comprising the amino acid sequence from amino acid 163 to amino acid 172 of SEQ ID NO:31; and

(f) the amino acid sequence encoded by the cDNA insert of clone bg140_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 77 to nucleotide 1624;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 390 to nucleotide 789;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bg465_2 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bg465_2 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 253 to amino acid 262 of SEQ ID NO:6;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

18. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 260 to amino acid 343;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising the amino acid sequence from amino acid 253 to amino acid 262 of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone bg465_2 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 48 to nucleotide 1055;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 216 to nucleotide 1055;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 494 to nucleotide 958;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bk291_3 deposited under accession number ATCC 98353;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bk291_3 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 85 to amino acid 94 of SEQ ID NO:8;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

21. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 188 to amino acid 306;

(c) fragments of the amino acid sequence of SEQ ID NO:8 comprising the amino acid sequence from amino acid 85 to amino acid 94 of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone bk291_3 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 64 to nucleotide 1197;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 828;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bp537_4 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bp537_4 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:10;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 255;

(c) fragments of the amino acid sequence of SEQ ID NO:10 comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone bp537_4 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 581 to nucleotide 1534;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 928 to nucleotide 1510;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cs431_2 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cs431_2 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 154 to amino acid 163 of SEQ ID NO:12;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

27. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 150 to amino acid 310;

(c) fragments of the amino acid sequence of SEQ ID NO:12 comprising the amino acid sequence from amino acid 154 to amino acid 163 of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone cs431_2 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

29. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 29 to nucleotide 2227;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1334 to nucleotide 2227;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 746;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cw976_1 deposited under accession number ATCC 98353;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cw976_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 361 to amino acid 370 of SEQ ID NO:14;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 239;

(c) the amino acid sequence of SEQ ID NO:14 from amino acid 119 to amino acid 733;

(d) fragments of the amino acid sequence of SEQ ID NO:14 comprising the amino acid sequence from amino acid 361 to amino acid 370 of SEQ ID NO:14; and

(e) the amino acid sequence encoded by the cDNA insert of clone cw976_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

32. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 364 to nucleotide 777;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 1 to nucleotide 636;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cw1233_3 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cw1233_3 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment

comprising the amino acid sequence from amino acid 64 to amino acid 73 of SEQ ID NO:16;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

33. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 91;

(c) fragments of the amino acid sequence of SEQ ID NO:16 comprising the amino acid sequence from amino acid 64 to amino acid 73 of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone cw1233_3 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 619 to nucleotide 1434;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 520 to nucleotide 1323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone dg1_1 deposited under accession number ATCC 98353;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone dg1_1 deposited under accession number ATCC 98353;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 131 to amino acid 140 of SEQ ID NO:18;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

36. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 235;

(c) fragments of the amino acid sequence of SEQ ID NO:18 comprising the amino acid sequence from amino acid 131 to amino acid 140 of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone dg1_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.

38. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2063 to nucleotide 2290;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2276 to nucleotide 2290;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2037 to nucleotide 2405;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ep234_1 deposited under accession number ATCC 98353;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ep234_1 deposited under accession number ATCC 98353;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone ep234_1 deposited under accession number ATCC 98353;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone ep234_1 deposited under accession number ATCC 98353;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:20;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

39. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 69;

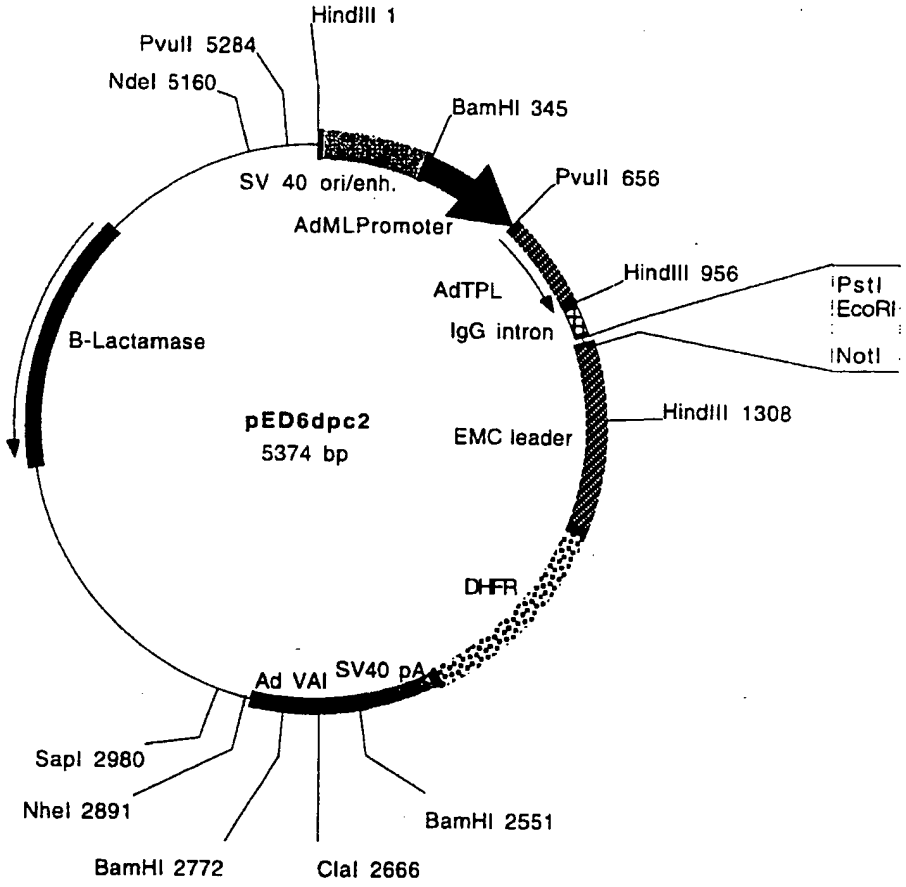
(c) fragments of the amino acid sequence of SEQ ID NO:20 comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone ep234_1 deposited under accession number ATCC 98353;

the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:19.

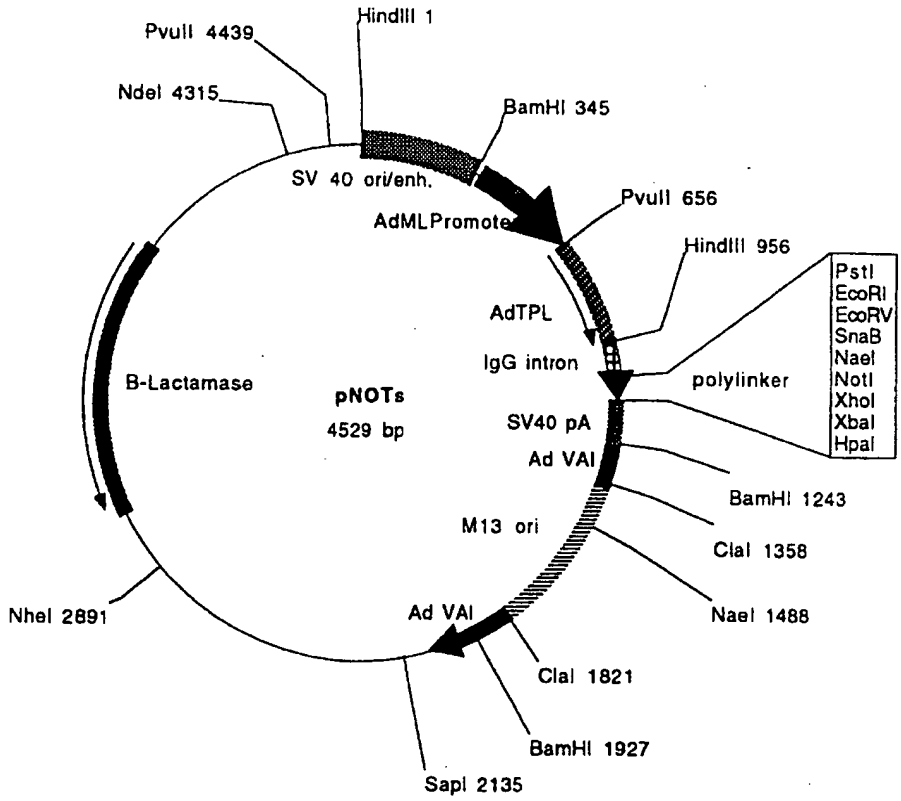
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI